

Part of 28/A

VS GGSINSGDYVWSWIRQHPKGLDCIGYIYSGSTYNP SLKSRVTISVDTSKNQF FLKLTSVTAADTAVYYCARSTVNPNGWFDPMGGGTLVTYSS (SEQ ID NO: 23)

CDR1

CDR2

CDR3

FIG. 1

GTCTCTGGTG GCTCCATCAA CAGTGGTGAT TACTACTGGA GCTGGATCCG CCAGCACCCA GGGAGGGCC TGGACTGCAT TGGGTACATC TATTACAGTG GGAGCACCTA CTACACCCG  
TCCCTCAAGA GTGAGTTAC CATATCAGTA GACAGTCTA AGATCAGTT CTTCCTGAAG CTGACTCTG TGA CTGCCC GGACACGGCC GTGTATTACT GTGGAGATC TACGGTGGTA  
AATCCGGGGT GGTTCGACCC CTGGGGCCAR GGAACCTGG TCACCGTCTC CTCA (SEQ ID NO: 3)

FIG. 2

TTTCQASDINNYLWVFQKPGKAPK VLIHDSNLETGGPSRFSGSGTDFTFTISGLQPEDATYYCQDYESLPLTFGGGTKEIKRTVAAPSVFIFPPSDEQ (SEQ ID NO: 24)

CDR1

CDR2

CDR3

FIG. 3

ACCATCACTT GCCAGGCGAG TCAGGACATT AACAACTATT TAAATTGGTT TCAGCAGAAA CCAGGGAAG CCCT AAGGTCCTGA TCCACGATGC ATCCAATTG GAAACAGGG  
GCCCATCAAG GTTCAGTGA AGTGGATCTG GGACA GATTTACTT TCACCATCAG CGGCTGCAG CCTGAAGACA TTGCACATA TTATTGTCAA CAGTATGAAA GTCTC CCACCTCACTT  
TCGGCGGAGG GACCAAGGTG GAGATCAAA (SEQ ID NO: 4)

FIG. 4

VSGGSINSGDYVWSVIRQHPGKLEWIGSIYSGNIFYNPSLKSRVTISLDTSKNQFSLKSSVTAADIAVCYCARNIVTTGAFDINGGGTMVTYSS (SEQ ID NO: 25)

CDR1 CDR2 CDR3

FIG. 5

GTCTCTGGTG GCTCCATCAA CAGTGGTGAT TACTACTGGA GCTGGATCCG CCAGCACCCA GGGAGGGGCC TGGAGTGGAT TGGGTCCATC TATTACAGTG GGAACACCTT CTACAACCCG  
TCCCTCAAGA GTGAGTTAC CATATCACTA GACAGGTCTA AGAACCAATT CTCCTGAAG CTGAGTTCTG TGA CTGCCG GACACGGCC GTGTGTTACT GTGGAGAAA TATAGTACT  
ACGGGTGCTT TTGATATCTG GGGCCAAGGG ACAATGGTCA CCGTCTCTTC A (SEQ ID NO: 5)

FIG. 6

TTTCQASQDIT IYLNWYQKPKAPKLLINDASSLETGVPLRFSGSGSDTFTFTISSLOPEDIATYYCQYDHLPLTFGGGTVKVAIKRTVAAPSVFIFPPSDEQ (SEQ ID NO: 26)

CDR1 CDR2 CDR3

FIG. 7

ACCATCATT GTACGGCGAG TCAGGACATT ACCATTATT TAAATTGTA TCAACAGAAA CCAGGAAAG CCCCT AGGTCCTGA TCAACGACGC ATCCAGTTTG GAAACAGGGG  
TCCATTAAAG GTTCAGTGA AGTGGATCTG GGACA GATTTTACTT TCACCATCAG CAGCCTGCAG CCTGAAGATA TTGCAACATA TTACTGTCAA CAGTATGATC ATCTC CCGCTCACTT  
TCGGCGGCGG GACCAAGGTG GCGATCAAA (SEQ ID NO: 6)

FIG. 8

VSGGSISSG DYYW T V I R Q H P G K G L E N I G Y I Y Y S G N T Y Y N P S L K S R V S M S I D T S E N Q F S L K L S S V T A A D T A V Y Y C A R K P V T G G E D Y W G G G T L V T V S S (SEQ ID NO: 27)

CDR3

CDR2

CDR1

**FIG. 9**

G T C T C T G G T G G T C C A T C A G C A G T G G T G A T T A C T A C T G G A C C A C C C A G G A A G G G C C T G G T A C A T C T G G T A C A G T G G A C A C C C T A C T A C A C C C G  
 T C C C T C A A G A G T C G A G T T C C A T G C A A T A G A C A G T T C T C C T G A A G C T G A G C T C T G T G A C T G C C G G G A C A G G C C G T G T A T T A C T G T G G A G A A A A C C A G T G A C T  
 G G G G G G A G G A C T A C T G G G G C C A G G G A A C C C T G G T C A C C G T C T C C T C A (SEQ ID NO: 7)

**FIG. 10**

T I T C Q A S Q D I S N Y L N W Y Q K P G K A P K L L I Y D A S N L E T G V P S R F S G S G T D F T F T I S S L Q P E D I V G Y Y V Q R Y E S L P C G F G G G T K L E I K R T V A P S V F I F P P S D E Q (SEQ ID NO: 28)

CDR3

CDR2

CDR1

**FIG. 11**

A C C A T C A C T T G C A G G C G A G T C A G G A C A T T A G T A C T A T T T A A T T G G T A T C A G C A G A A A C C A G G A A G C C C T A N G C T C C T G A T C A C A T G C T T C C A A T T T G G A A C A G G G G T C C C A T C A A G  
 G T T C A G T G G A G T G G A T C T G G A C A T C A G C A G C C T G C A G C C T G A A G A T G T T G G A A C A T A T G T C T G T C A A C A G T A T G A G A G T C C C G T G C G G T T T T G G C C A G G G  
 G A C C A A A C T G G A G A T C A A A (SEQ ID NO: 8)

**FIG. 12**

VSGGSI<sup>NSG</sup>DF YWSVIRQHPCKGLEVIGYIYSGSYNPSLKSRYT<sup>Ms</sup>JdP<sup>SKNDF</sup>SLKL ISVTAADTAVYYCA<sup>T</sup>SLYYGGGMDVWGQGT<sup>TVTVSS</sup> (SEQ ID NO: 29)

CDR1

CDR2

CDR3

**FIG. 13**

GTCTCTGGTG GCTCCATCAA CAGTGGTGAT TTCTACTGGA GCTGGATCCG CCAACACCCA GGGAGGGCC TGGAGTGGAT TGGGTACATC TATTACAGTG GGAGCACCTA CTACAACCCG  
TCCCTCAAGA GTCGAGTTAC CATGTCAATA GACCCGTCTA AGACCAAGTT CTCCTGAAA CTGATCTCTG TGA CTGCCC GGACACGGCC GTTTATTACT GTGGGACNTC CCTTTACTAT  
GGCGGGGGTA TGGACGTCTG GGGCCAAGG ACCACGGTCA CCGTCTCCTC A (SEQ ID NO: 9)

**FIG. 14**

TTTCAASD<sup>ISN</sup>NL<sup>NHYYQK</sup>Rg<sup>NAPKLL</sup>YDASNLETGVP<sup>SRS</sup>SGSGSDTFT<sup>FTIS</sup>NLPEDIA<sup>TYQCH</sup>HYD<sup>HL</sup>PNWTFGGG<sup>TKVEXKRTVA</sup>PSVFI<sup>PPSDEQ</sup> (SEQ ID NO: 30)

CDR1

CDR2

CDR3

**FIG. 15**

ACCATCACTT GCCAGGCGAG TCAGGACATT AACACTATT TGAATTGGTA TCAGGAGAG CNGGGAGCG CCGCT AAAC<sup>TCC</sup>TGTA TCTAGCATGC ATCCAATTG GAAACAGGGG  
TCCCATCAAG GTTCAGTGA AGTGGATCTG GGACA GATTTTACTT TCACCATCAA CAGCCTGCAG CCTGAAGATA TTGGACATA TTATTGCAA CACTATGATC ATCTC CCGTGGACGT  
TCGGCCAAGG GACCAAGGTG GAANTCAAA (SEQ ID NO: 10)

**FIG. 16**

VSGGSINNGDYYSVIRQHPGKLEWIGHIYYSGSTYYIPSLKSR T TISVDTSKNQFSLKLN SVTAADIAVYYCARGTIVTTYYFDYWGGGTTVTYSS (SEQ ID NO: 31)  
CDR1 CDR2 CDR3

**FIG. 17**

GTCTCTGGTG GCTCCATCAA CAATGGTGAT TACTACTGGA GCTGGATCCG CCAGCACCCA GGAAGGGCC TGGAGTGGAT TGGGCACATC TATTACAGTG GGAGCACCTA CTACATCCCC  
TCCCTCAAGA GTCGAACTAC CATATCAGTA GACAGTCTA AGAACCAATT CTCCTGAAG CTGAACCTGT TGACTGCCGC GGACACGGCC GTGTATTACT GTGCGAGAGG GACAGTAACT  
ACGTACTACT TTGACTACTG GGGCCAGGGA ACCCTGGTCA CCGTCTCCTC A (SEQ ID NO: 11)

**FIG. 18**

TTTCRASDSISSYLNWYQKPKAPKLLIYAASSLQSGVPSRFSGSGGTDFTLTISLQPEDFATYYCQQ GyRTPPECSFGGTKLEIKRTVAAPSVIFPPPSDEQ (SEQ ID NO: 32)  
CDR1 CDR2 CDR3

**FIG. 19**

ACCATCACTT GCCGGGCAAG TCAGAGCATT AGCAGCTATT TAAATGGTA TCAGCAGAAA CCAGGGAAG CCCCT AAGCTCCTGA TCTATGCTGC ATCCAGTTTG CAAAGTGGGG  
TCCCATCAAG GTTCAGTGGC AGTGGATCTG GGACA GATTTCATC TCACCATCAG CAGTCTGCAA CCTGAAGATT TTGCAACTTA CTACTGTCAA CAGGGTTACA GAACC CCTCCGGAGT  
GCAGTTTTTG CCAGGGGACC AAGCTGGAGA TCAAA (SEQ ID NO: 12)

**FIG. 20**

VSGGSVSSG D Y Y W S W I R Q P P G K G L E W I G H L Y Y S G N T N Y N P S L K S R V T I S L D T S K N Q F S L K L S S V T A A D I A V Y Y C A R D F L I G S F F D Y W G G T L V T V S S (SEQ ID NO: 33)

CDR1 CDR2 CDR3

FIG. 21

GTCTCTGGTG GCTCCGTCAG CAGTGGTGAT TACTACTGGA GCTGGATCCG GCAECCCCCA GGGAGGGGAC TGGAGTGGAT TGGACATCTC TATTACAGTG GGAACACCACAA CTACAACCCC  
TCCCTCAAGA GTCGAGTCAC CATATCATT GACAGTCCA AGAACAGT CTCCTGAAG CTGAGCTCTG TGACCGCTGC GGACACGGCC GTGTATTACT GTGGAGAGA TTTTGTGACT  
GGTTCCTTCT TTGACTACTG GGGCCAGGGA ACCCTGGTCA CCGTCTCCTC A (SEQ ID NO: 13)

FIG. 22

TITCQASQD I S N Y L N W Y Q Q K P G K A P K L L I N D A S D L E T G V P S R I S G S G T D F T F T I S N L O P E D I A T Y Y C Q Q Y D S L P L T F G G T K V E I R R T V A A P S V F I F P P S D E Q (SEQ ID NO: 34)

CDR1 CDR2 CDR3

FIG. 23

ACCATCACTT GCCAGGGGAG TCAGGACATA AGCACTATT TAAATTGGTA TCAGCAGAAA CCAGGGAAG CCCCT AAGCTCCTGA TCAACGATGC ATCCGATTG GAAACAGGGG  
TCCCATCAAG GATCAGTGA AGTGGATCTG GGACA GATTTTACTT TCACCATCAG CAACCTGCAG CCTGAAGATA TTGCAACATA TTACTGTCAA CAATATGATA GTCTC CCGGTCACCT  
TCGGCGGAGG GACCAAGGTG GAGATCAGA (SEQ ID NO: 14)

FIG. 24

VS GGSV YSGDYYSWIRQPPKGLWIGYIYSGSTNYPNPSLKS RVTISVDTSKNQFSLKLS SSVTAADTAVYYCARD SILGATNYWGGLTVTVSS (SEQ ID NO: 35)

CDR1

CDR2

CDR3

FIG. 25

GTCTCTGGTG GCTCCGCTCTA CAGTGGTGAT TACTACTGGA GCTGGATCCG GCAGCCCCC GGAAGGGAC TGGAGTGGAT TGGGTATATC TATTACAGTG GGAGCACCAC TTAACAATCCC  
TCCCTCAAGA GTCGAGTCAC CATATCAGTA GACAGTCCA AGAACCAAGT CTCCTGAG CTGAGCTCTG TGACCGCTGC GGACACGGCC GTGTATTACT GTGCGAGAGA CTCCTACTG  
GGAGCTACCA ACTACTGGGG CCAGGGAACC CTGGTCACCG TCTCCTCA (SEQ ID NO: 15)

FIG. 26

TTTCQASD XISNYL XWYQKPKGKPK XLI S DASNLETGVP SRFSGSGSGT XXIFTISSLPEDIATYHcXQYXS LPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQ (SEQ ID NO: 36)

CDR1

CDR2

CDR3

FIG. 27

ACCATCACTT GCCAGGGCAG TONGGACATT AATAACTATT TANATTGGTN TCAGCAGAAA CCAGGGAAG CCCCT AAATCCCTGA TCTCCGATGC ATCCAATTTA GAAACAGGGG  
TCCCATCGAG GTTCAGTGA AGTGGATCTG GGACA GANTNTACTT TCACCATCAG CAGCCTGCAG CCTGAAGATA TTGCNACATA TCACTGTGCA CAGTATNATA GTCTC CCGCTCACTT  
TCGGCGGAGG GACCAAGGTA GAGATCAAA (SEQ ID NO: 16)

FIG. 28

VSGGSVSSGDYYWTVIRQSPGKGLEWIGHYYSGNTNYPNPKSR<sup>CDR1</sup>LTISIDTSK<sup>CDR2</sup>TQFSLKLSVTAADTAIYYCVRDRVTGAFDIVGGGTMTVSS (SEQ ID NO: 37)  
<sup>CDR3</sup>

**FIG. 29**

GTCTCTGGTG GCTCCGTCAG CAGTGGTGAT TACTACTGGA CCTGGATCCG GCAGTCCCA GGAAGGGAC TGGAGTGGAT TGGACACATC TATTACAGTG GGAACACCAA TTATAACCCC  
 TCCCTCAAGA GTGACTCAC CATATCAATT GACAGTCCA AGACTCAGTT CTCCTGAAG CTGAGTTCTG TGACCGCTGC GGACACGGCC ATTTATTACT GTGTGGGAGA TCGAGTGACT  
 GGTGCTTTTG ATATCTGGG CCAAGGGACAATGGTCACCG TCTCTTCA (SEQ ID NO: 17)

**FIG. 30**

TTTCQASQDISNYLWYQQKPKAPKLLIYDASNLETGVPSRFSGSGSGTDFTFTISSLOPEDIATYF<sup>CDR1</sup>CoHF<sup>CDR2</sup>DHLPLAFGGGKVEIKRTVAAPSVFIPPPSDEQ (SEQ ID NO: 38)  
<sup>CDR3</sup>

**FIG. 31**

ACCATCACTT GCAGGGGAG TCAGGACATC AGCACTATT TAAATTGGTA TCAGCAGAAA CCAGGGGAAG CCCCT AAATCCTCGA TCTACGATGC ATCCAATTG GAAACAGGGG  
 TCCCATCAG GTTCAGTGA AGTGGATCTG GGACA GATTTTACTT TCACCATCAG CAGCCTGCAG CCTGAAGATA TTCTGTCAATA TTCTGTCAA CACTTTGATC ATCTC CCCTCGCTT  
 TCGGGGGAGG GACCAAGGTG GAGATCAAA (SEQ ID NO: 18)

**FIG. 32**



*Amino Acid Sequences and Structure of Human Heavy Chain Derived from EGFR-Specific Hybridomas*

Human $\gamma 2$	CDR1	CDR2	CDR3	ASTKGPSVFPPPLAPCSRSTST (SEQ ID NO: 19)
4-31	VSGGSSGGYYWSWIRQHPGKGLEWIGYIYYSGSTYNPNP	SLKSRVTISVDTSKNQFSLKSSVTAADTAVYYCAR	STVWNP	VFDP
E1.1	N-D	DC	F-I	VGQGLVTVSS (SEQ ID NO: 42)
E2.4	N-D	S-N-F	L-C	VGQGTWTVSS (SEQ ID NO: 43)
E2.5	D-T	N	SM-I-E	VGQGLTVTVSS (SEQ ID NO: 44)
E6.2	N-DF	M-I-P	TSLYYGG	VGQGTWTVSS (SEQ ID NO: 45)
E6.4	NN-D	I-T	GVTVTY	VGQGTWTVSS (SEQ ID NO: 46)

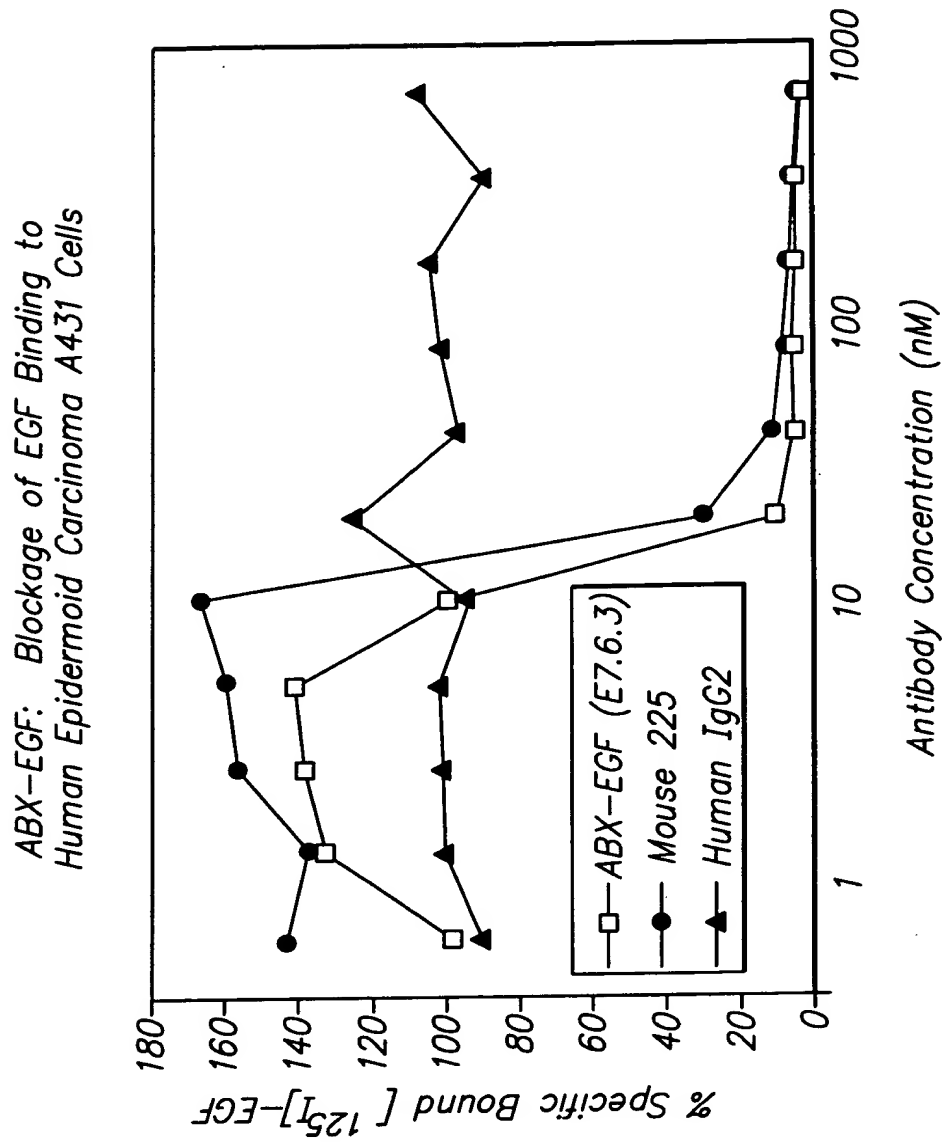
CDR1	CDR2	CDR3	(SEQ ID NO: 22)
4-61	VSGGSVSGSYYWSWIRQPPGKGLEWIGYIYYSGSTYNPNP	SLKSRVTISVDTSKNQFSLKSSVTAADTAVYYCAR	DFLTGSF FDY (SEQ ID NO: 47)
E2.11	D	HL-N	VGQGTWTVSS (SEQ ID NO: 48)
E6.3	Y-D	DSILGA	VGQGLTVTVSS (SEQ ID NO: 49)
E7.6.3	D-T	S-I-N	VGQGTWTVSS (SEQ ID NO: 49)

**FIG. 33**

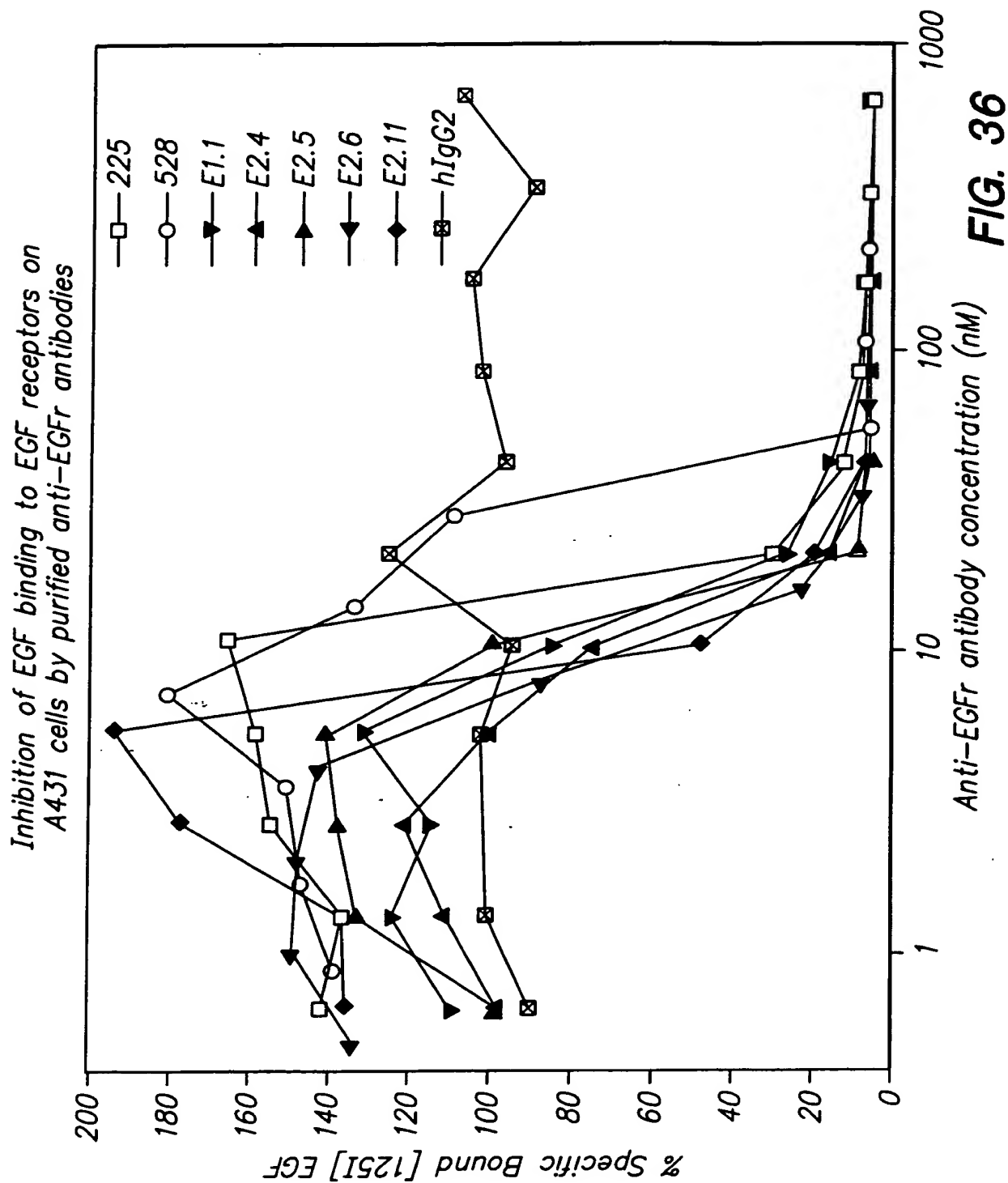
Amino Acid Sequence and Structure of Human Kappa Chain Derived from EGFR-Specific Hybridomas

	V <sub>K</sub> SEGMENT			J <sub>K</sub> SEGMENT	
	CDR1	CDR2		CDR3	
V <sub>K</sub> (018)	TITQASQDTSNYLN	NYQQKPGKAPKLLIYDASNLEIGVPSRFGSGSGTDFTFITSSLPEDIAIYYQQQYDNL		RTVAAPSVFIFPPSDEQ	(SEQ ID NO: 41)
Human Ck					(SEQ ID NO: 20)
EGF.1.1.K	N--F--N--	V--H--G--	ES--	LTGGGKVEIK	(SEQ ID NO: 24)
EGF.2.4.K	TI--	N--S--L--	H--	LTGGGKVAIK	(SEQ ID NO: 26)
EGF.2.5.K			VG--V--ES--	CGGGGKLEIK	(SEQ ID NO: 28)
EGF.2.11.K		N--D--I--	S--	LTGGGKVEIR	(SEQ ID NO: 34)
E6.2.K	N--R--N--	R--N--X--S--	H--H--	VTGGGKVEK	(SEQ ID NO: 30)
E6.3.K	X--N--X--	X--S--	H--X--XS--	LTGGGKVEIK	(SEQ ID NO: 36)
E6.4.K*	R--S--S--	A--S--QS--	GYRT-PE	CSGGGKLEIK	(SEQ ID NO: 32)
*012 Gene 21			F--	LAFGGKVEIK	(SEQ ID NO: 38)
E7.6.3.K			F--HF--H--		

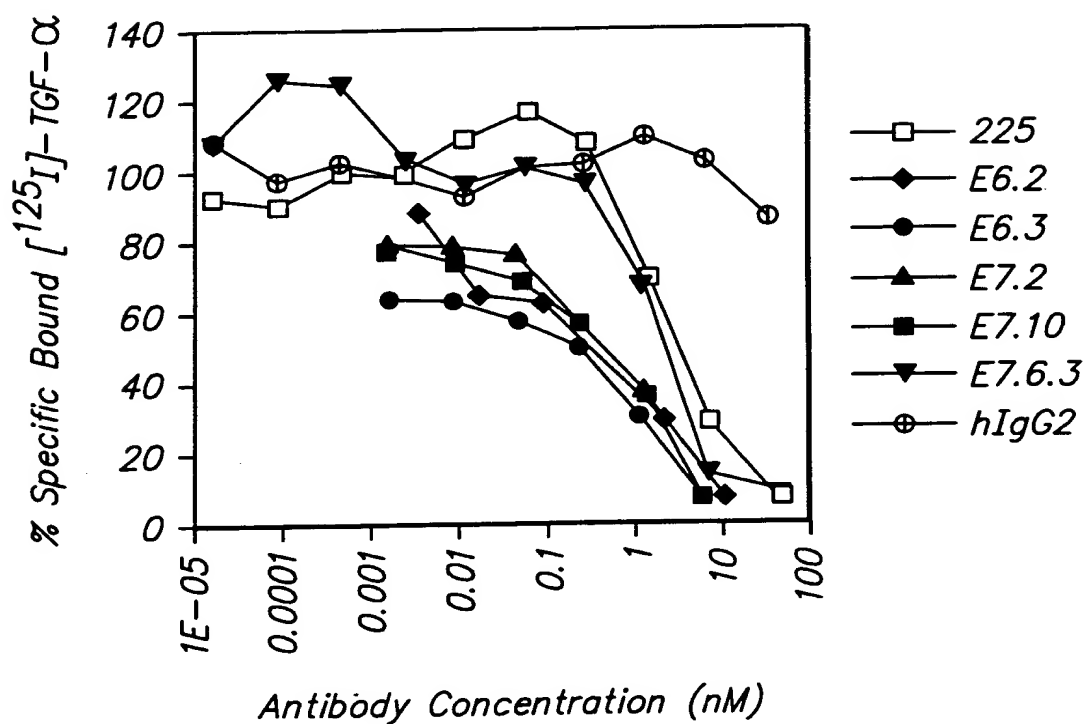
FIG. 34



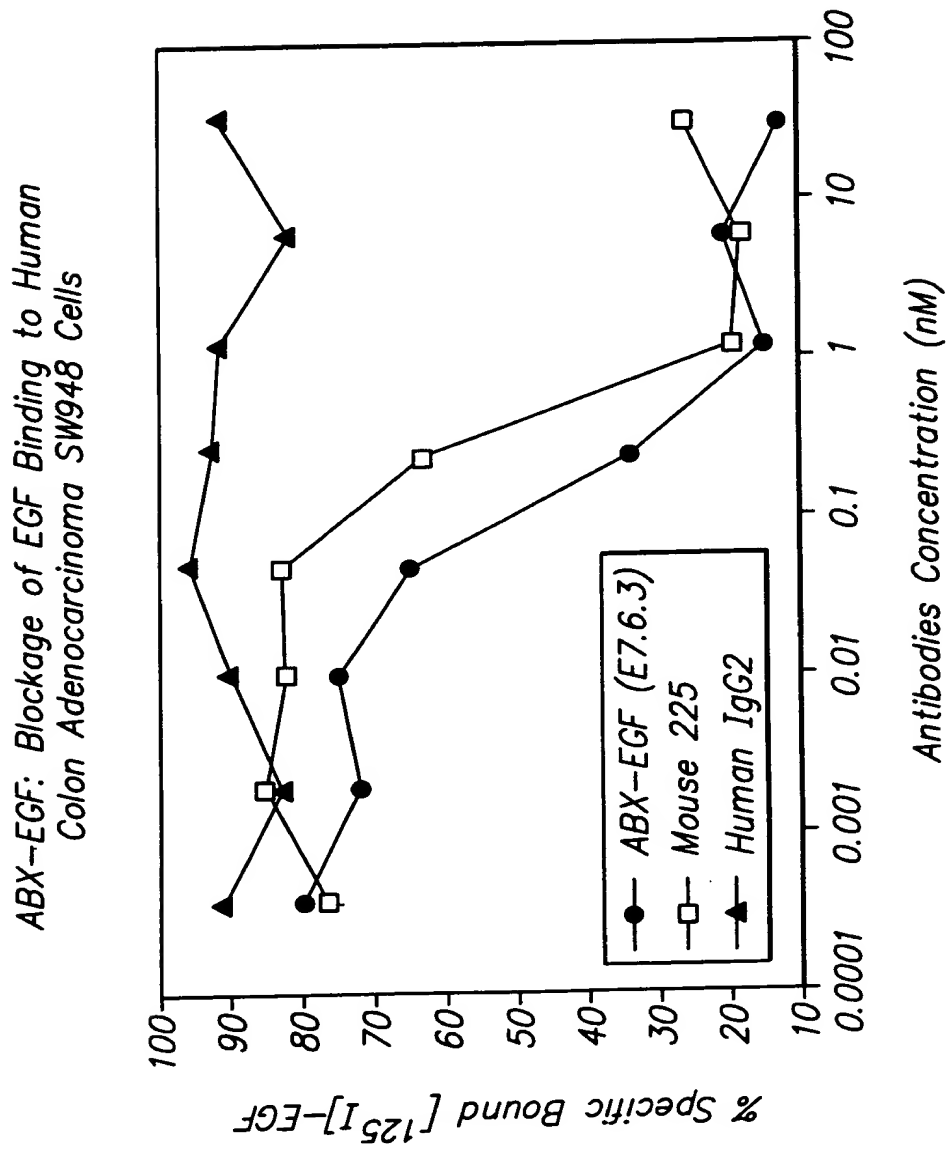
**FIG. 35**



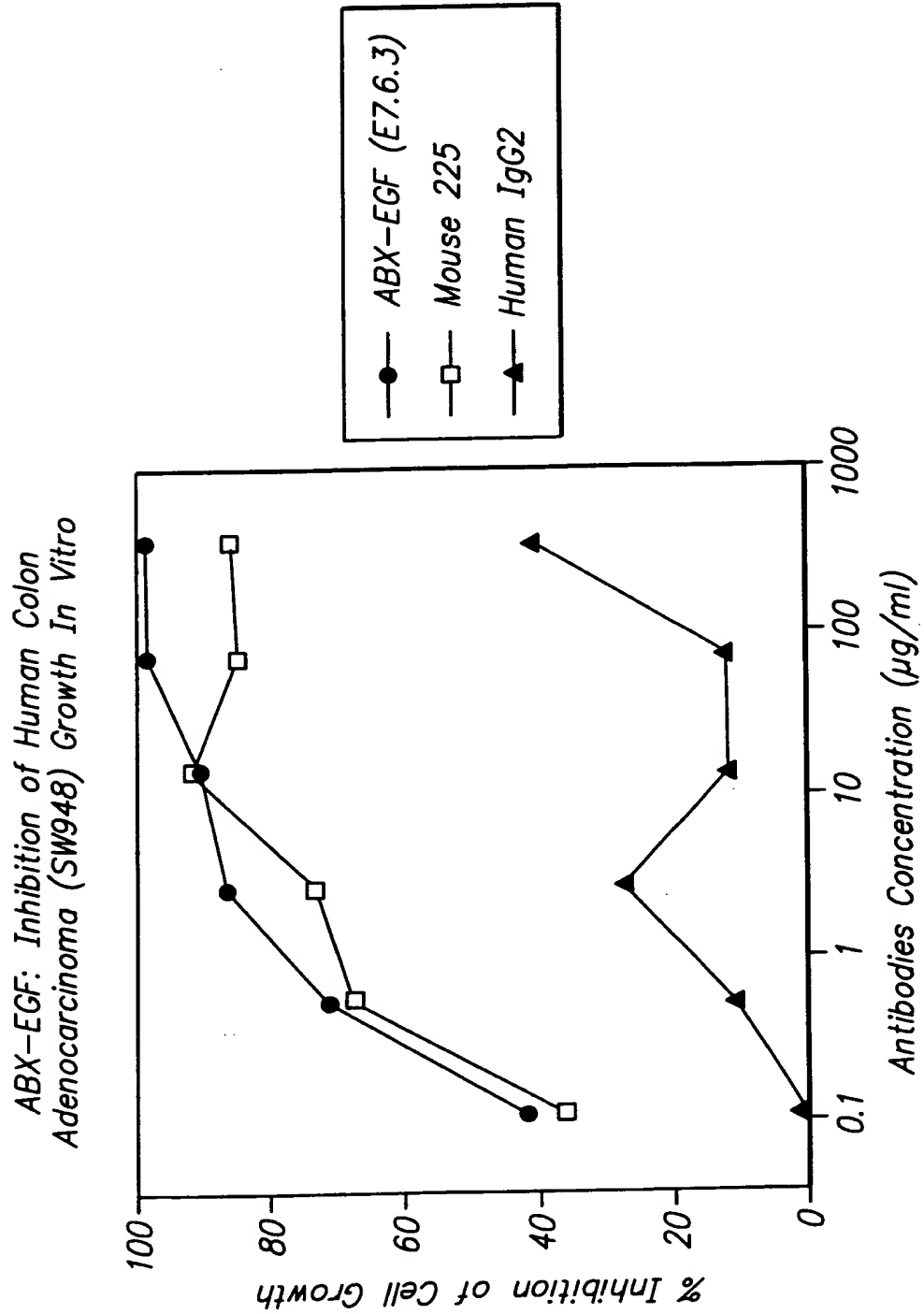
*Inhibition of TGF- $\alpha$  binding to A431 cells  
 by anti-EGF receptor antibodies*



**FIG. 37**



**FIG. 38**



**FIG. 39**

ABX-EGF: Inhibition of Human Epidermoid  
 Carcinoma Growth in Nude Mice

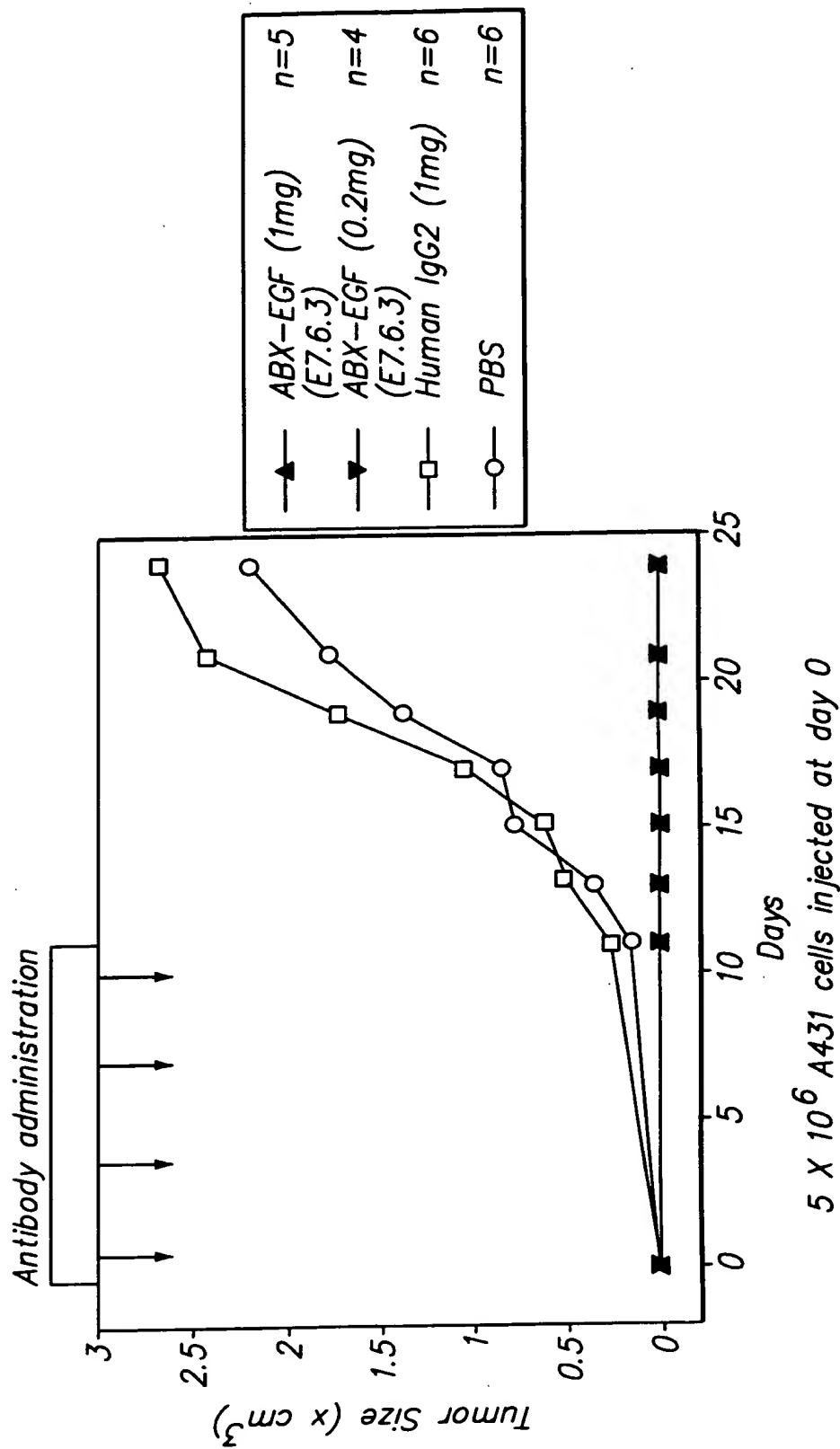


FIG. 40



*Inhibition of Human Epidermoid Carcinoma  
 Formation in Nude Mice by ABX-EGF*

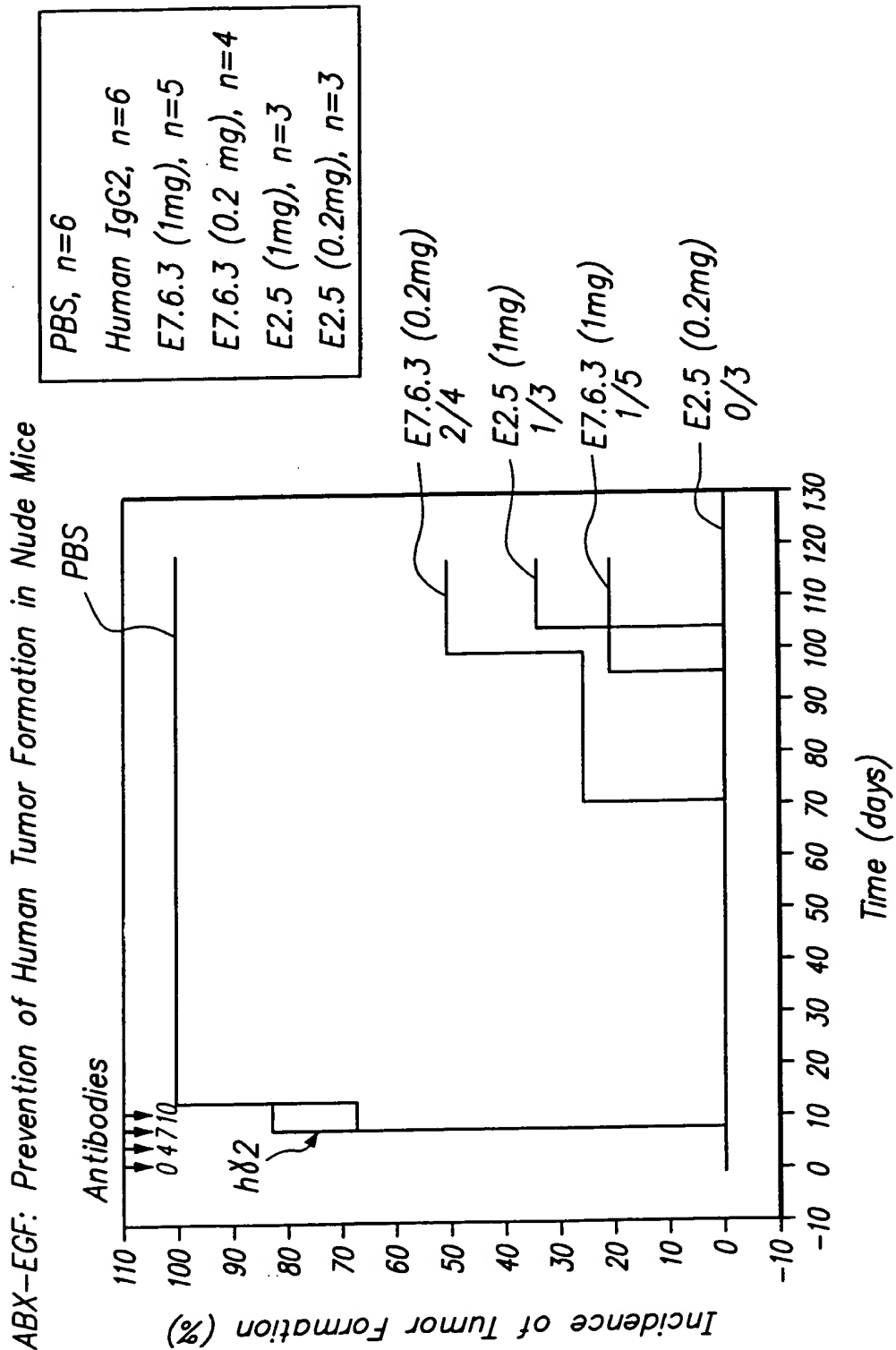
<i>Treatment</i>	<i>Dose (mg)</i>	<i>Tumor Formation<sup>b</sup> (incidence)</i>	<i>Tumor size<sup>c</sup> (cm<sup>3</sup>)</i>
PBS		6/6	1.376
Human IgG2 <sup>a</sup>	1	6/6	1.727
E7.6.3	1	0/5	0
	0.2	0/4	0
E2.5	1	0/3	0
	0.2	0/3	0
E1.1	1	0/3	0

<sup>a</sup> control human myeloma IgG2

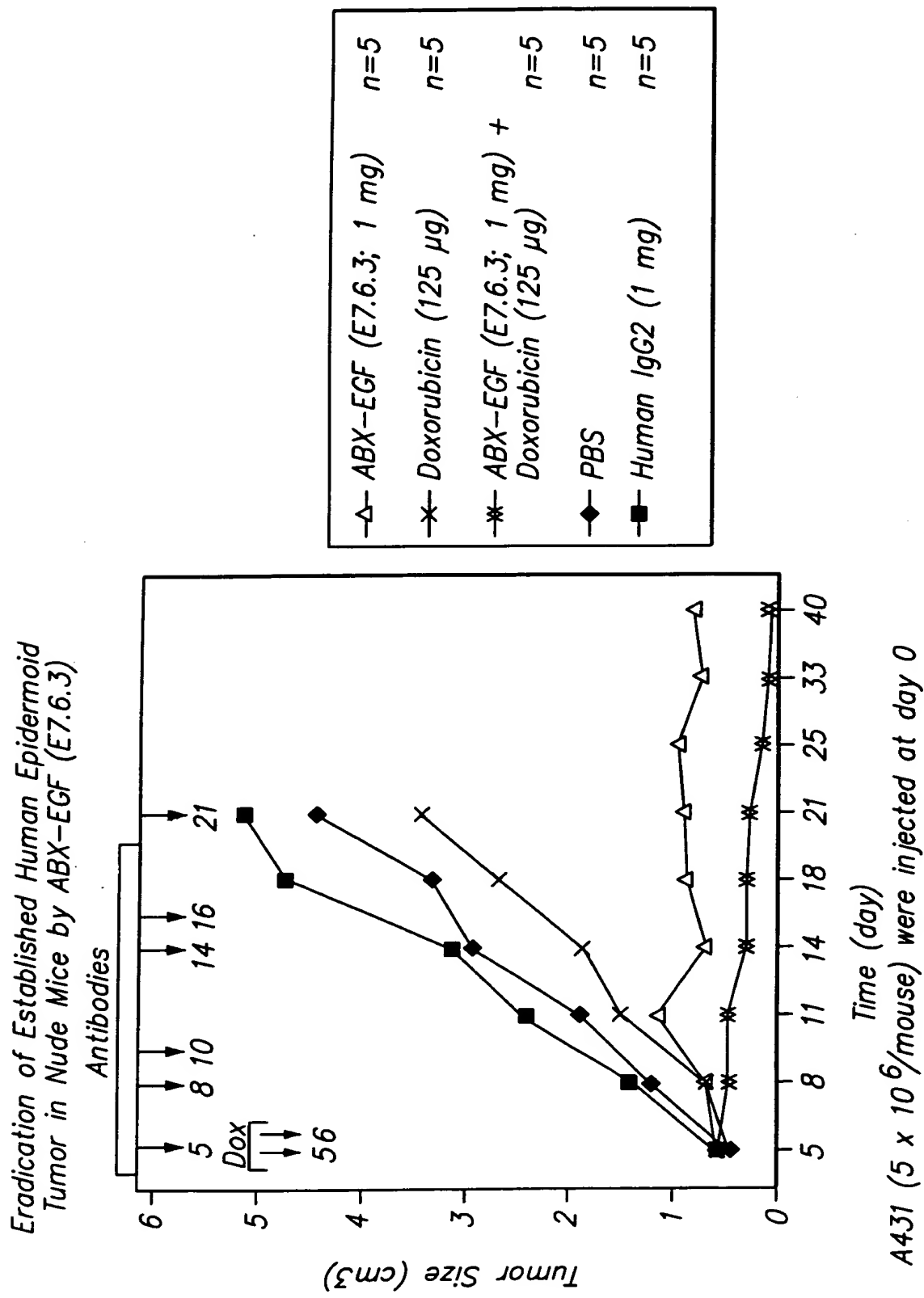
<sup>b</sup> incidence determined 19 days post tumor inoculation

<sup>c</sup> tumor size measured 19 days post tumor inoculation

**FIG. 41**



**FIG. 42**



**FIG. 43**

Eradication of Established Human Epidermoid Tumor in Nude Mice by ABX-EGF (E2.5)

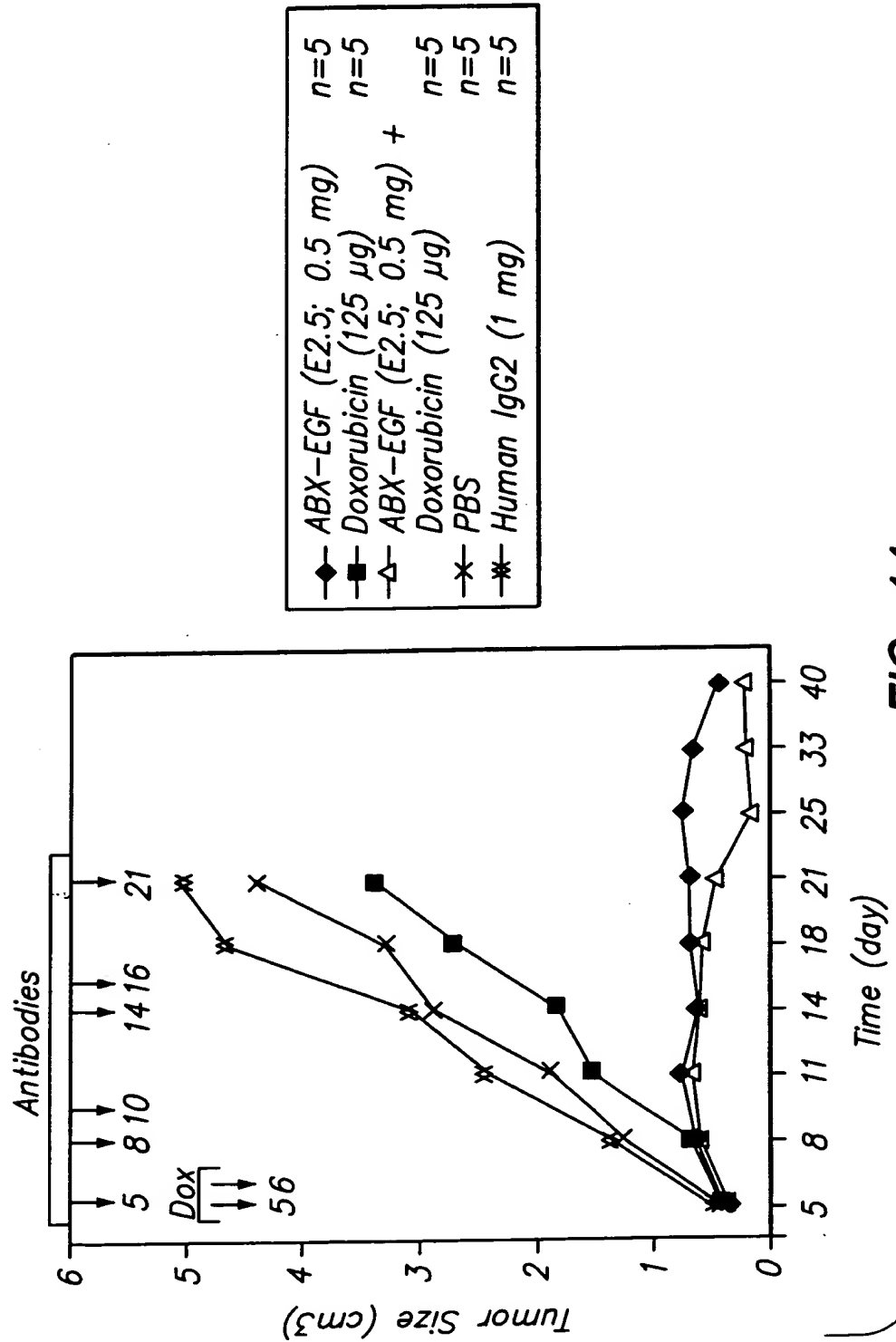
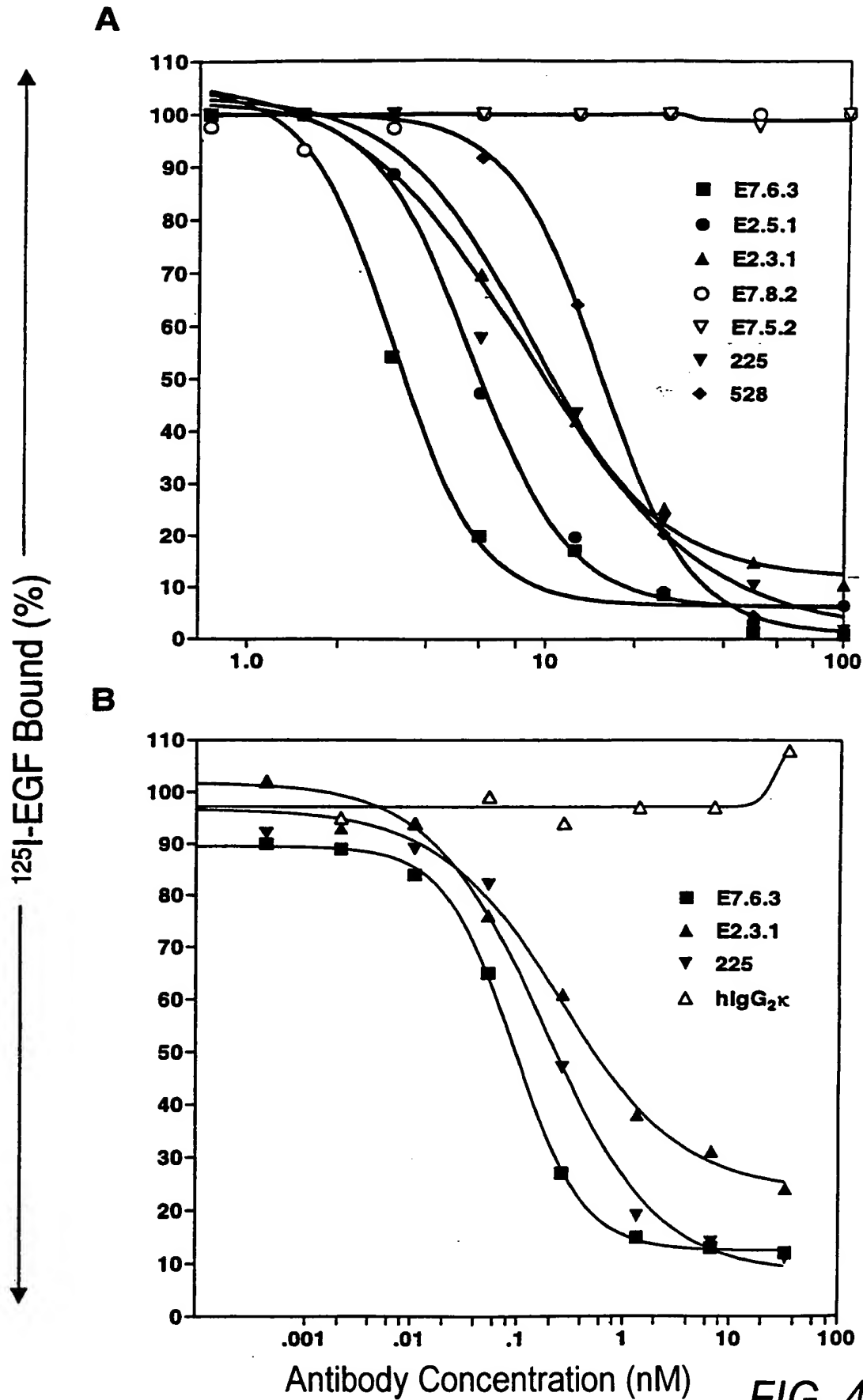


FIG. 44



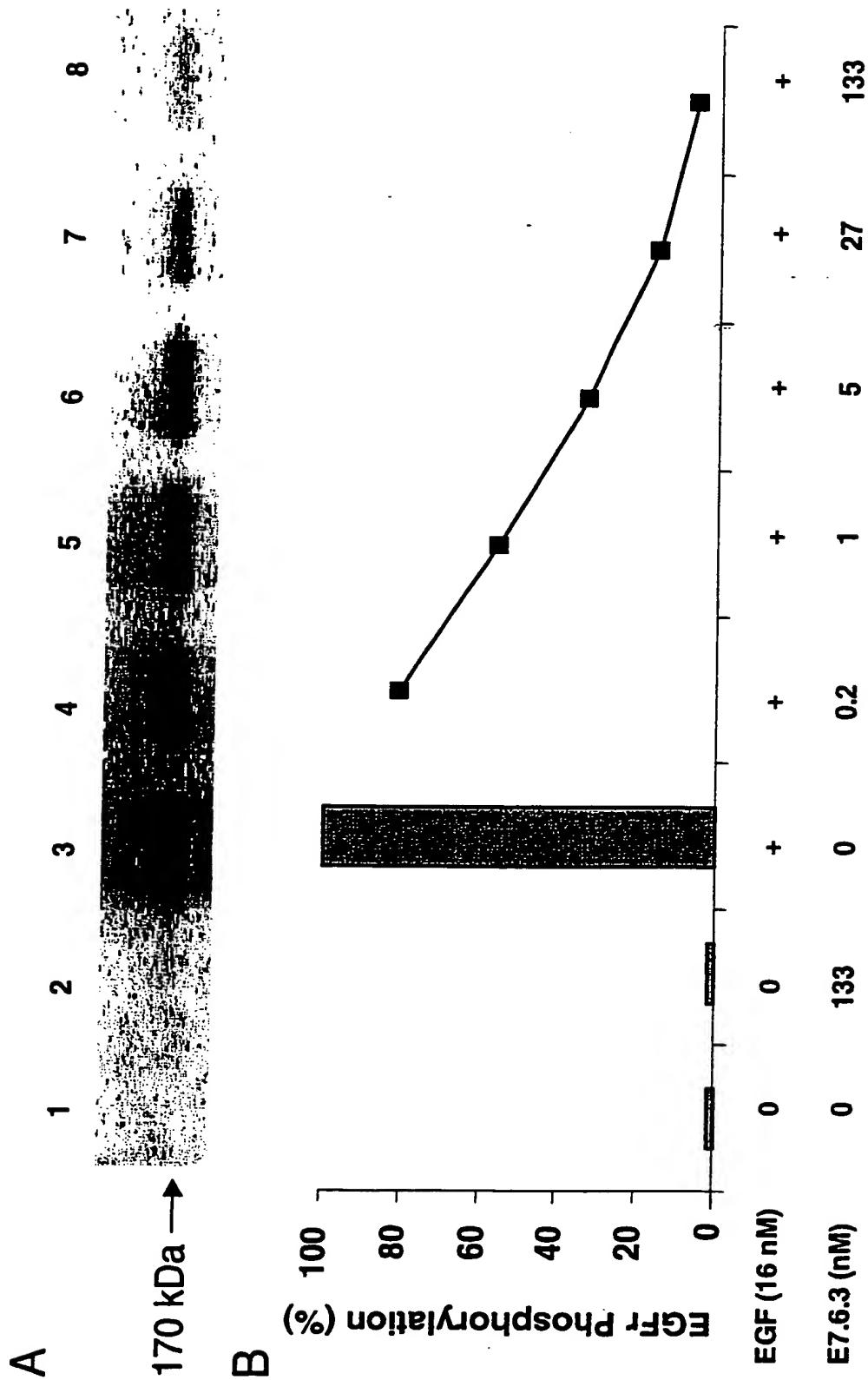
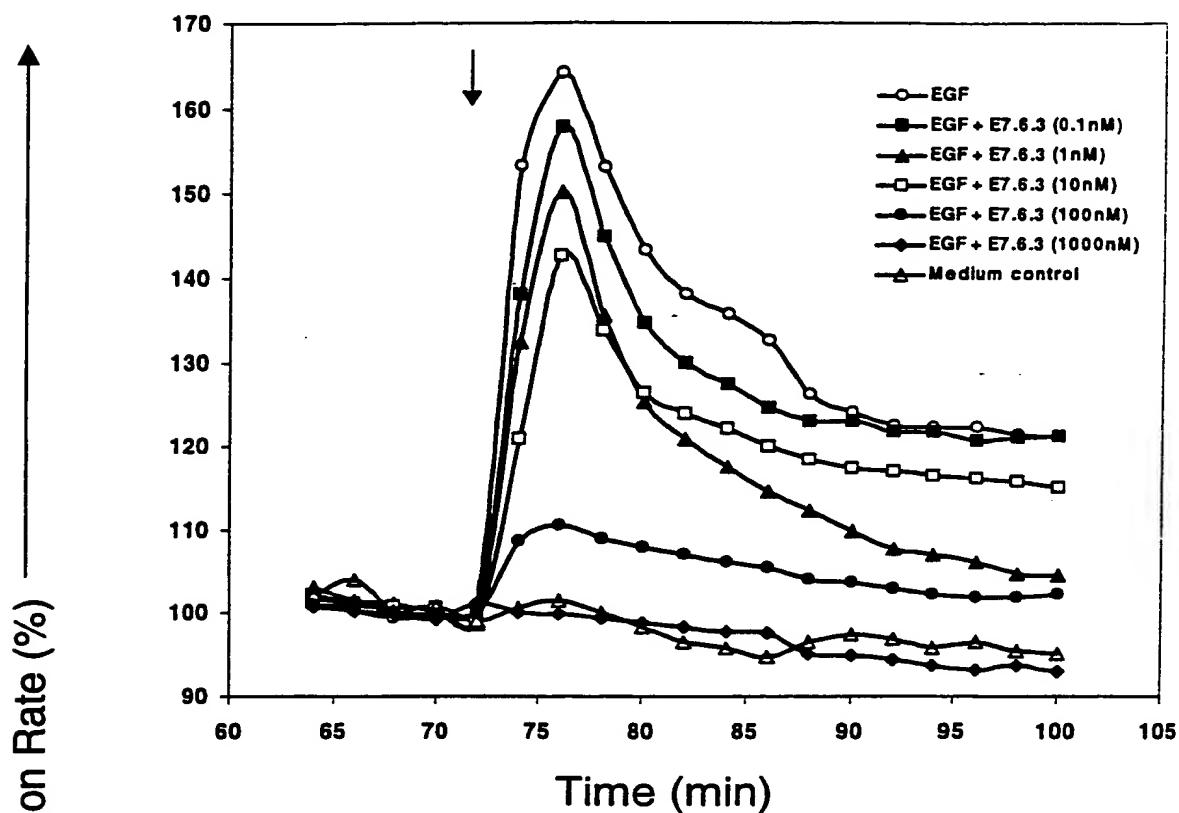
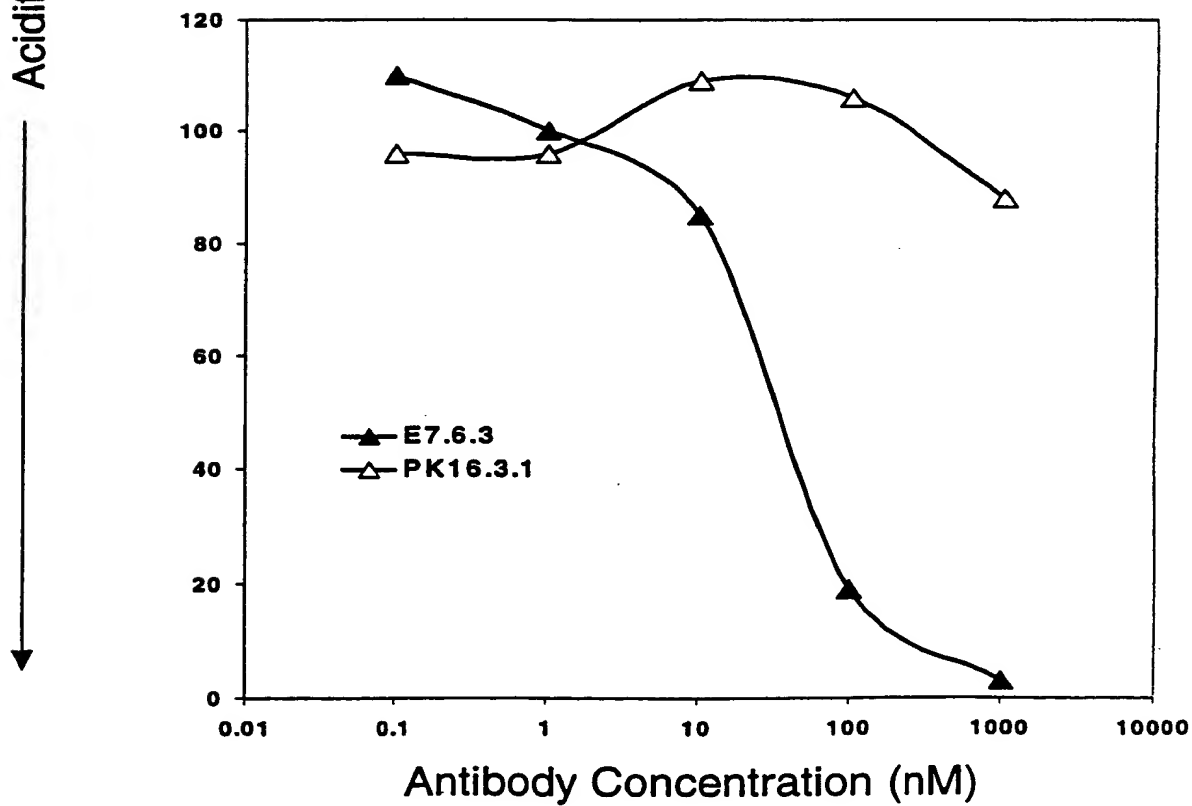


FIG. 46

**A**



**B**



**FIG. 47**

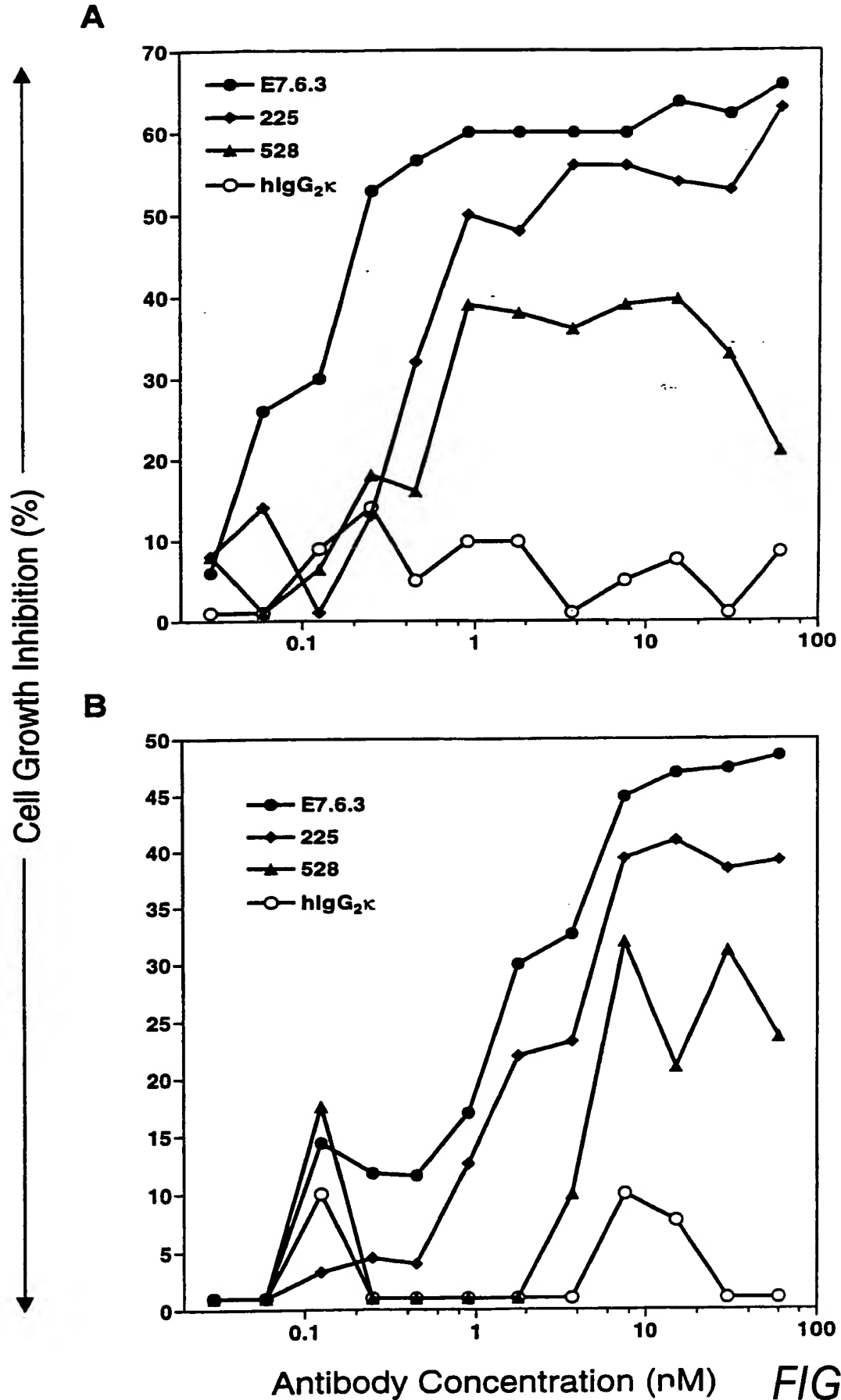


FIG. 48



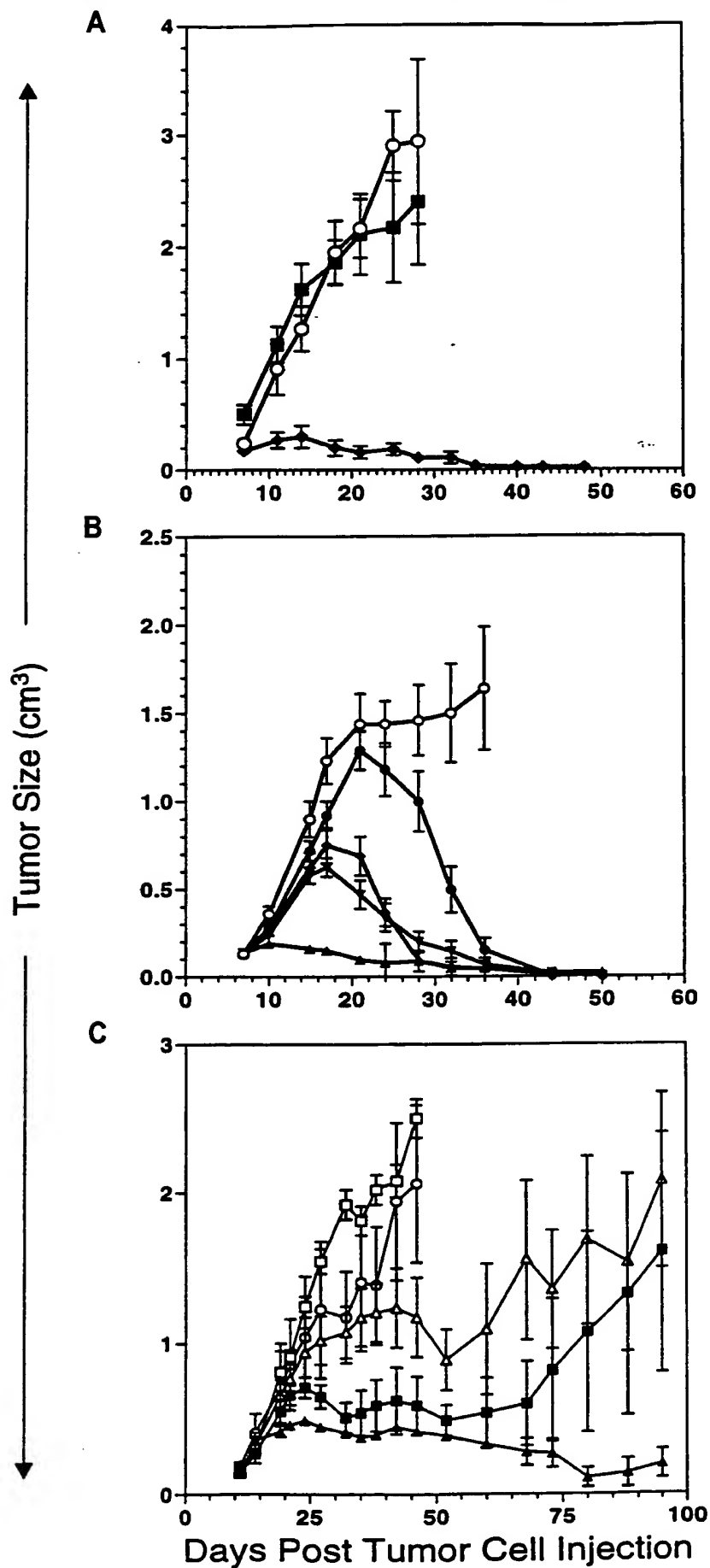


FIG. 49

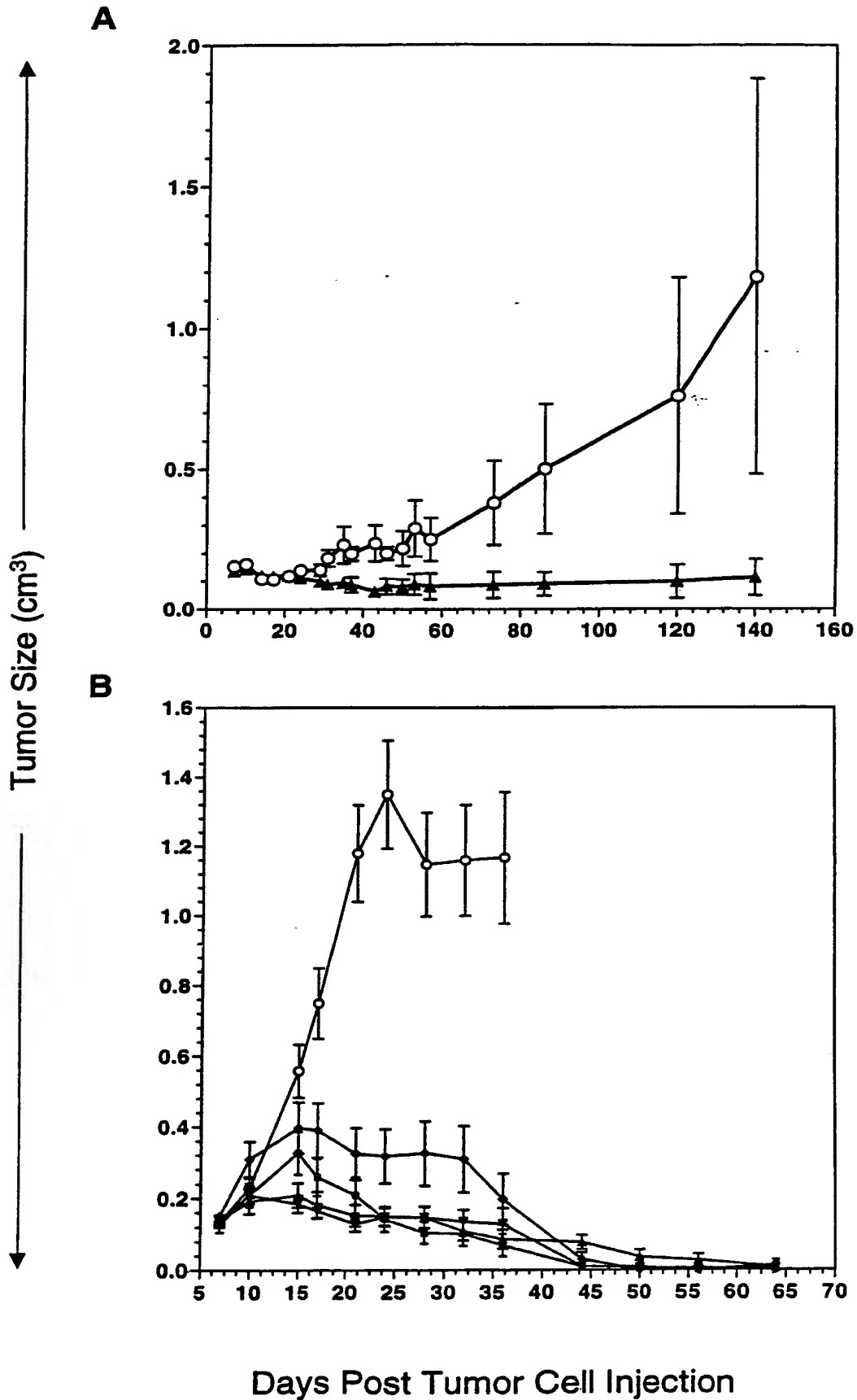


FIG. 50

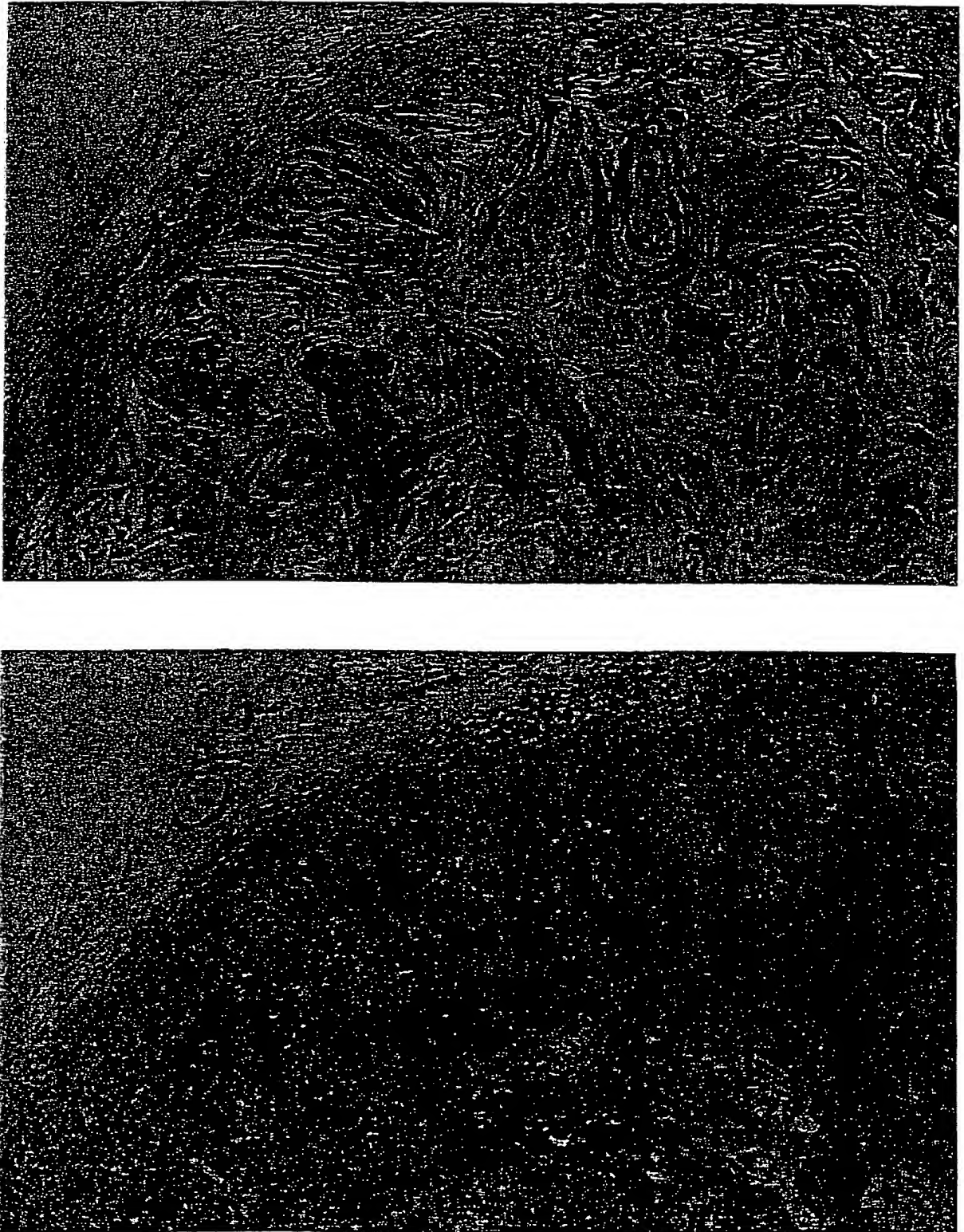


FIG. 51

Time (day)	Incidence of Tumor Formation		
	PBS	PK16.3.1 (1 mg)	E7.6.3 (0.2 mg) E7.6.3 (1 mg)
0	0/5	0/5	0/10
3	4/5	0/5	0/10
8	4/5	3/5	0/10
10	5/5	5/5	0/10
25	5/5	5/5	0/10
100	ND	ND	0/10
250	ND	ND	0/10

FIG. 52

Tumor-free Mice on Day 60			
Treatment (dose/injection)	Total Dose	Total No. of Mice	%
None		71	0
Control IgG <sub>2</sub> κ (1 mg)	6 mg	16	0
E7.6.3 (1 mg)	6 mg	50	100
E7.6.3 (0.5 mg)	3 mg	20	95
E7.6.3 (0.25 mg)	1.5 mg	5	60
E7.6.3 (0.2 mg)	1.2 mg	19	26
E7.6.3 (0.1 mg)	0.6 mg	20	65
E7.6.3 (0.05 mg)	0.3 mg	15	7

FIG. 53

# Inhibitory Effects of E7.6.3 on EGF-induced Tyrosine-phosphorylation and Degradation of EGFr in Cultured A431 Cells

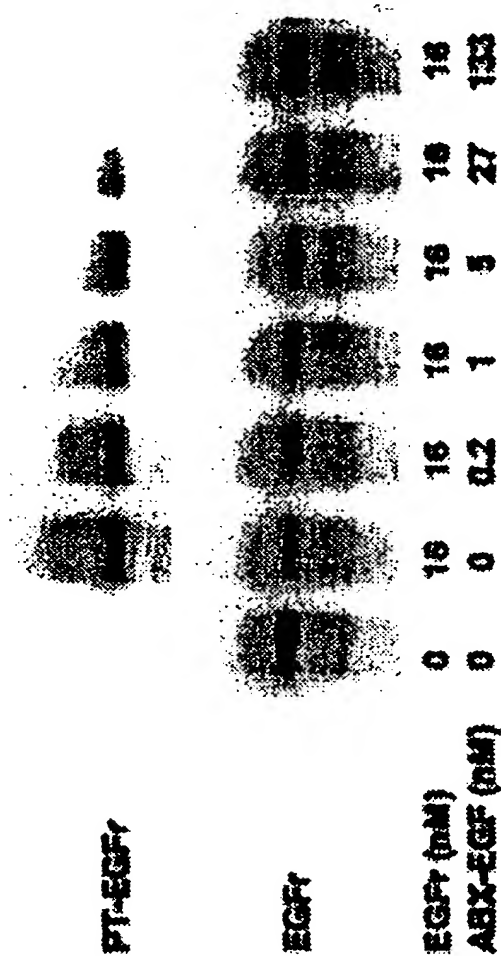


FIG. 54

# Preliminary results obtained comparing Inhibitory Effects of E 7.6.3 and 225 on EGF-induced Tyrosine-phosphorylation and Degradation of EGFr in Cultured A431 Cells



Preliminary results obtained comparing  
 Effects of EGF, ABX-EGF and 225 on  
 Tyrosine-phosphorylation and Degradation of EGFr in  
 Cultured A431 Cells

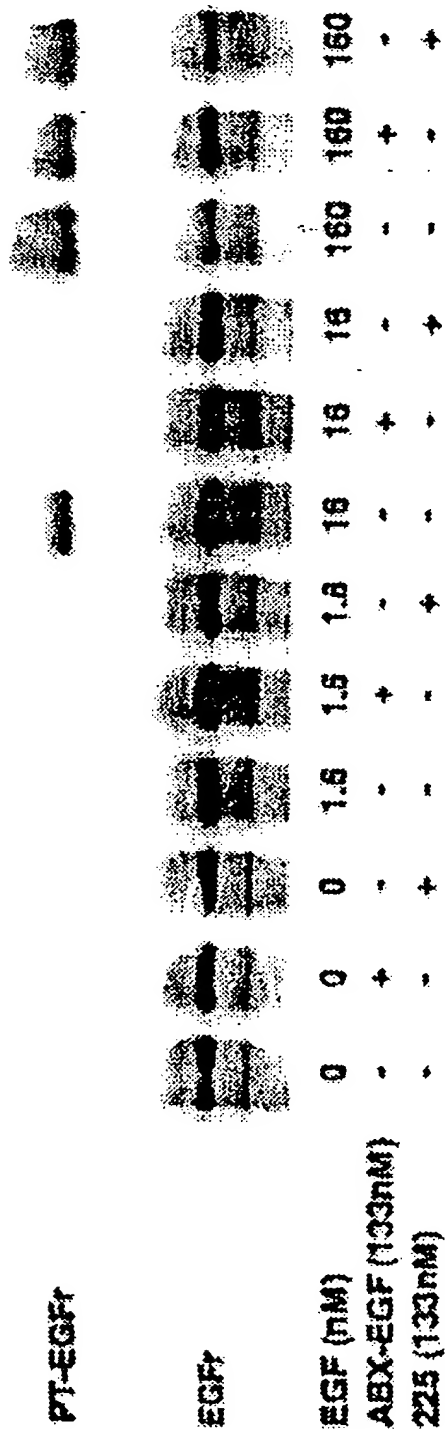


FIG. 56



E20.1MG30.Seq Sequ nce

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GCGATCCAGC	CTTTTAGGTC	CATGCGNTTC	TCTGTGNAG	CGTCTGGATT	50
A I Q P	F R S	M P F	S C X A	S G F	
CCCCITCAGT	AGNINIGGCA	TGCACTGGGT	CCGCCAGGCT	CCAGGCAAGG	100
P F S	X X G M	H W V	R Q A	P G K G	
GGCTGGAGTG	GGTGGCAGTT	ATATGGIATG	ATGGAAGTAA	TAAATACTAT	150
L E W	V A V	I W Y D	G S N	K Y Y	
GCAGACTCCG	TGAAGGGCCG	ATTCACCATC	TCCAGAGACA	ATTCCAAGAA	200
A D S V	K G R	F T I	S R D N	S K N	
CACGCTGTAT	CTGCAAATGA	ACAGACTGAG	AGCGGAGGAC	ACGGCTGTGT	250
T L Y	L Q M N	R L R	A E D	T A V Y	
ATTACTGTC	<del>GACATTTTC</del>	<del>GAGGCGT</del>	<del>AGGCGT</del>	<del>AGGCGT</del>	300
Y C A	R F L	E W L P	F D Y	W G Q	
<del>GGGCGTGTAT</del>	<del>CTGCAAATGA</del>	<del>ACAGACTGAG</del>	<del>AGCGGAGGAC</del>	<del>ACGGCTGTGT</del>	350
G T L V	T V X	S D S	T K G P	S V F	
CNCCCTGGCG	CCCTGCTTCC	AGGAGCACCC	TGNGANAGCA	CANANGGCC	400
X L A	P C F Q	E H P	X X A	X X A P	
CTGGGACTGN	CTGNTACAAG	GACTINCTTTC	CCTONAACCN	GGTGACCNIN	450
G T X	X Y K	D X F P	S N X	V T X	
TCTGGGAAA	CTCAGNGCNC	NICTINNATNA	C	(SEQ ID NO: 19)	481
S W E T	Q X X	S X X		(SEQ ID NO: 55)	

FIG. 57

E20.1VK.Seq Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GGAACTTTIN	GGTTCGNC	TTTTGGAGNC	AGACCCANCA	TCACITGTCTG	50
G T F X	F A P	F G X	R P X I	T C R	
GGCGAGTCAG	GGCATTAGCA	ATTTTTTAGC	CTGGTTTCAG	CAGAAACCAG	100
A S Q	G I S N	F L A	W F Q	Q K P G	
GGATAGCCCC	TAAGTCCCIG	ATCTATGCTG	CATCCACTTT	GCAAAGTGGG	150
I A P	K S L	I Y A A	S T L	Q S G	
GTCCCATCAA	AGTTCACCGG	CAGTGGATAT	GGACAGATT	TCACTCTCAC	200
V P S K	F T G	S G Y	G T D F	T L T	
CATCAGCAGC	CTGCAGCCTG	AAGACTTTGC	AACTTATTAT	TGTCACAAT	250
I S S	L Q P E	D F A	T Y Y	C Q Q Y	
ATAATGTTTA	CCCATTCACT	TTCCGCCCTG	GGACCAAAGT	GGATATCAAA	300
N V Y	P F T	F G P G	T K V	D I K	
CGAACTGIGG	CTGCACCATC	TGTCCTTCATC	TTCCCGCCAT	CTGATGAGCC	350
R T V A	A P S	V F I	F P P S	D E P	
AGTTGAAATC	TGGAACTGCC	TCTGTGTGIGT	GCCTGCTGAA	TAACTTCTAT	400
V E I	W N C L	C C V	P A E	L L S	
CCCAGACAGG	CCAAAGTACA	GTCGAAGGTG	GATAACGCCN	CNNITGGCGG	450
Q R G	Q S T	V E G G	R X	X W R	
NNTCCTTTN	CTCNCCTC	CTCNCCTC	CTCTCNCNA	(SEQ ID NO: 20)	489
X P F X	X P S	S X X	L S X	(SEQ ID NO: 56)	

FIG. 58

E20.3MG30.Seq S quence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
AAGCCIGTGTG	CCTCAGTGCA	GGTCTCTGC	AAGGCTTCTG	GATACACCTT	50
K P V A	S V Q	V S C	K A S G	Y T F	
CACCAGTTAT	GATATCAACT	GGGTGGGACA	GGCCACTGGA	CAAGGGCTTG	100
T S Y	D I N W	V R Q	A T G	Q G L E	
AGTGGATGGG	ATGGATGAAC	CCTAACAGTG	GTAACACAGG	CTATGCACAG	150
W M G	W M N	P N S G	N T G	Y A Q	
AAGTTCCAGG	GCAGAGTCAC	CATGACCAGG	AACACCTCCA	TAAGCACAGC	200
K F Q G	R V T	M T R	N T S I	S T A	
CTACATGGAG	CTGAGCAGCC	TGAGATCTGA	GGACACGGCC	GTGTATTACT	250
Y M E	L S S L	R S E	D T A	V Y Y C	
DNI					
GTGGGAGAGG	AGGCCCCAT	AGCAGTGGCT	GGACCTTCTT	TGACTACTGG	300
A R G	G P Y	S S G W	T F F	D Y W	
GGCCAGGGAA	CCCTGGTCAC	CGTCTCTCA	GGCTTNCACC	AAGGGCCCAT	350
G Q G T	L V T V	S S	A L H Q	G P I	
CGGTCCTCCC	CCTGGCGCCC	TGCTCCAGGA	GCACCTCCCA	GAGCACANIC	400
G L P	P G A L	L Q E	H L P	E H X X	
NNCCCTTGGG	CTGGCTGGNN	CAAGGACTCT	TTCCCCNAAC	CCCGGNTGA	(SEQ ID NO: 21) 449
P L G	C L X	Q G L F	P X T	P X	(SEQ ID NO: 57)

FIG. 59

# E20.3VK.Seq Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TTTGAACCTT	TCTTGGGCGT	GTCTCTGGGC	GCGAGGGCCA	CCATCAACTG	50
F E P F	X A V	S L G	A R A T	I N C	
CAAGTCCAGC	CAGCGTGTTC	TATACANCTC	CAACAATAAG	AACTGCTTAG	100
K S S	Q R V L	Y X S	N N K	N C L A	
CTTGGTACCA	GCAGAAACCA	GGACAGCCTC	CTAAGCTGCT	CATTCTACTG	150
W Y Q	Q K P	G Q P P	K L L	I Y W	
ACATCTACCC	GGGAATCCGG	GGTCCCCTGC	CGATTTCAGT	GCAGCGGGTC	200
T S T R	E S G	V P A	R F S G	S G S	
TGGGACAGAT	TTCACTCTCA	CCATCAGCAG	CCTGCAGGCT	GAAGATGTTG	250
G T D	F T L T	I S S	L Q A	E D V A	
CAGTTTATTA	CTGTTCAGCA	TATTATAGTA	CTCCACTCAC	TTTCGGGGGA	300
V Y Y	C Q Q	Y Y S T	P L T	F G G	
GGGACCATGG	TGGAGATCAA	GCGAAGCTGT	GCTGCACCAT	CTGTCTTCAT	350
G T M V	E I K	R T V	A A P S	V F I	
CTTCCCAGCA	TCTGATGAGC	CNGINIGAAA	TCTGGAACTG	CCTCTGTTTG	400
F P P	S D E P	V	N L E L	P L F V	
TGTGCCCTGC	TGAATAACTT	CTATCCCAGA	GAGGCCAAAG	TACCAGTGG	450
C P A	E	L L S Q R	G Q S	T S G	
AGGTGGATAA	(SEQ ID NO: 22)				460
R W I	(SEQ ID NO: 58)				

FIG. 60

### E20.8.1MG30.Seq Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
CNGCCTGTGA	GGTCNIGCG	ACTCTCCIGT	GCAGCGTCTG	GATTCATCTT	50
X P V R	S X R	L S C	A A S G	F I F	
CAGTAGNIAT	GGCATGCACT	GGGTCCGGCA	GGCTCCAGGC	AAGGGGCTGG	100
S X Y	G M H W	V R Q	A P G	K G L E	
AGTGGGTGGC	AATTATATGG	TATGATGGAA	GTAATAAATA	CTATGCAGAC	150
W V A	I I W	Y D G S	N K Y	Y A D	
TCGGTGAAGG	GOOGATTAC	CATCTCCAGA	GACAATTCCA	AGAACAAGCT	200
S V K G	R F T	I S R	D N S K	N T L	
GTATCTGCAA	ATGAACAGCC	TGAGAGCCCA	GGACAAGGCT	GIGTATTACT	250
Y L Q	M N S L	R A E	D T A	V Y Y C	
GTGCGAGAGA	CGGGGGGCA	CGGIGGTTTC	TGCTTCTGA	CTACTGGGGC	300
A R D	G G P	R W F L	A S D	Y W G	
CAGGCAACCC	TGGTCACCGT	CTCTCAGCC	TCCACCAAGG	GOOCATCGGT	350
Q G T L	V T V	S S A	S T K G	P S V	
CTTCCCCCTG	GCGCCCTGCT	CCAGGAGCAC	OCTTCGAGAG	CACAGCGGCC	400
F P L	A P C S	R S T	L R E	H S G P	
CTGGGCTGOC	TGGTICAAGG	ACTACTTTCC	CCGAACCGGT	GACGGTGINC	450
G L P	G S R	T T F P	E P V	T V X	
GTGGAACTC	ATGAC	(SEQ ID NO: 23)			465
V G T H	D	(SEQ ID NO: 59)			

FIG. 61

E20.8.1MG18.Seq Sequ nc

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
AGICTCCAGA	CTCCCTGGIT	GTGICTCTGG	GCGAGAGGGC	CACCATCAAC	50
S L Q T	P W L	C L W	A R G P	P S T	
TGCAAGTCCA	GNCAGAGTAT	TTTATACAGC	TCCAACAATC	AAAAACTTCT	100
A S P	X R V F	Y T A	P T I	K N F L	
TAGCTTGGTA	CCAGCAGAAA	CCAGGACAGC	CTCCGAAGTT	GCTCATTTAC	150
A W Y	Q Q K	P G Q P	P K L	L I Y	
TGGGCATCTA	TTCCGGGAATC	CGGGGTCOCT	GACCGATTCA	GTGGCAGCGG	200
W A S I	R E S	G V P	D R F S	G S G	
GTCTGGGACA	GATTTCACCTC	TCACCATCAG	CAGCCTGCAG	GCTGAAGATG	250
S G T	D F T L	T I S	S L Q	A E D V	
TGGCAGTTTA	TTACTGTTCAG	CAGTATTATA	GIATTCCGTG	CACTTTIGGC	300
A V Y	Y C Q	Q Y Y S	I P C	T F G	
CAGGGGACCA	AGCTGGAGAT	CAAACGAAC	GTGGCTGCAC	CATCTGTCTT	350
Q G T K	L E I	K R T	V A A P	S V F	
CATCTTCCCG	CCATCTGATG	AGCAGTTGAA	ATCTGGAACT	GCCTCTGTG	400
I F P	P S D E	Q L K	S G T	A S V V	
TGIGCCTGCT	GAATAACTTC	TATCCCAGAA	AGGCCAAAGT	ACATGAAGGG	450
C L L	N N F	Y P R K	A K V	H E G	
TTCAAA	(SEQ ID NO: 24)				456
F K	(SEQ ID NO: 60)				

FIG. 62

### E20.11.2H Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GGCGTGGYCC	AGCCTGKAG	GTCCTGAGA	CCTCCTGIG	CAGCGTCTGG	50
G V X Q	P X R	S L R	L S C A	A S G	
ATTCAYCTTC	AGTARCTATG	GCATGCACTG	GGTCGCGCAG	GCTCCAGGCA	100
F X F	S X Y G	M H W	V R Q	A P G K	
AGGGGCTGGA	GTTGGGIGGCA	ATTATATGGT	ATGATGCAAG	TAGCAAATAC	150
G L E	W V A	I I W Y	D G S	S K Y	
TATGCAGACT	CCGTGAAGGG	CCGATTCAAC	ATCTCCAGAG	ACAATTCCAA	200
Y A D S	V K G	R F T	I S R D	N S K	
GAACAGCTG	TATCTGCAA	TGAACAGCCT	GAGAGCGCAG	GACACGGCTG	250
N T L	Y L Q M	N S L	R A E	D T A V	
TGTATTACTG	TGCGAGAGAC	GGGGGGGCAC	GGTGGTTTCT	CGCTTCTGAC	300
Y Y C	A R D	G G P R	W F L	A S D	
TACTGGGGCC	AGGGAAACCT	GGTCACCGTC	TCTCAGCCT	CCACCAAGGG	350
Y W G Q	G T L	V T V	S S A S	T K G	
CCCATCGGTC	TTCCCCCTGG	CGCCCTGCTC	CAGGAGCACC	TTCCGAGAGC	400
P S V	F P L A	P C S	R S T	F R E H	
ACAGCGGCCC	TGGGCTGCCT	GGTCAAGGAC	TACTTCCCCG	AAMCGGTGAC	450
S G P	G L P	G Q G L	L P R	X G D	
GGIGTCGTGG	AACTCAGGCG	CTCTGACCAG	NGGCGTGCAC	AATTCCCAGC	500
G V V E	L R R	S D Q	X R A Q	F P A	
NGTCCINAAG	GTIGAAATCG	TAANGGTICA	AA	(SEQ ID NO: 25)	532
V L K	V E I V	X V Q		(SEQ ID NO: 61)	

FIG. 63

20.11.2MG18.Seq Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
ACTCAGTCTC	CAGACTCCCT	GGCIGTGTCT	CTGGGCGAGA	GGGCCACCAT	50
T Q S P	D S L	A V S	L G E R	A T I	
CAACTGCAAG	TCCAGCCAGA	GIGTTTTATA	CGGCTCCAAG	AATCAGAACT	100
N C K	S S Q S	V L Y	G S K	N Q N Y	
ACTTAGCTTG	GTACCAGCAG	AAACCAGGAC	AGCCTCCTAA	GCTGGTCATT	150
L A W	Y Q Q	K P G Q	P P K	L L I	
TACTGGGCAT	CTACCCGGGA	ATCCGGGGTC	CCTGACCGAT	TCAGGGGCAG	200
Y W A S	T R E	S G V	P D R F	R G S	
CGGGTCTAGG	ACAGATTICA	CTCTCACCAT	CAGCAGCCTG	CAGGCTGAAG	250
G S R	T D F T	L T I	S S L	Q A E D	
ATGTGGCAGT	TTACTTCTGT	CACCAATATT	ATAGTACTCC	GTTGCAOGTTC	300
V A V	Y F C	H Q Y Y	S T P	W T F	
GGCCAAGGGA	CCAAGGTGGA	AATCAAACGA	ACTGTGGCTG	CACCATCTGT	350
G Q G T	K V E	I K R	T V A A	P S V	
CTTCATCTTC	CCGCCATCTG	ATGAGCAGTT	GAAATCTGGA	ACTGCTCTCTG	400
F I F	P P S D	E Q L	K S G	T A S V	
TTGTGTGGCT	GCTGAATAAC	TTGTATCCCA	GAAAGCCAAG	GACACGAAAG	450
V C L	L N N	L Y P R	K P R	T R K	
GTCAACCA	CCC	(SEQ ID NO: 26)			463
V X P T		(SEQ ID NO: 62)			

FIG. 64



# E20.18MG30.Seq Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
CGGATCCNC	CTGGNIGGTC	CCTGAGACTC	TCTGTGCAG	CGTCIGGATT	50
R D P P	G W S	L R L	S C A A	S G F	
CATCTTCANT	AACATATINCA	TGCACTGGGT	CCGOCAGGCT	CCAGGCAAGG	100
I F X	N Y X M	H W V	R Q A	P G K G	
GGCTGGAGTG	GGTGGCAATT	ATATGGTATG	ATGGAAGTAG	CAAATACTAT	150
L E W	V A I	I W Y D	G S S	K Y Y	
GCAGACTCCG	NGAAGGGCCG	ATTCAACATC	TCCAGAGACA	ATTCCAAGAA	200
A D S X	K G R	F T I	S R D N	S K N	
CACGCTGTAT	CTGCAAATGA	ACAGCCTGAG	AGCCGAGGAC	ACGGCTGATG	250
T L Y	L Q M N	S L R	A E D	T A D V	
TATTACTGIG	CGAGAGACGG	TTGGGCCACG	GTGGCTTCTC	GCTTCTGACT	300
L L C	E R R	L G H G	G F S	L L T	
ACTGGNGCNC	AGGGCAACNC	TGNCINACCG	TNTTCTTCAN	CCCTNTACNC	350
T G A Q	G N X	X X P	X S S X	L Y X	
AAGGGCCNCC	ATTNGGTCTT	TCCCCCTGG	NNNNCTGCT	CNATGNNNCA	400
R A X	I X S F	P P G	X P A	X X X T	
CCCTNCGACA	NONACAN	(SEQ ID NO: 27)			417
L R X	X X	(SEQ ID NO: 63)			

FIG. 65

# E20.18VK.Seq Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TTGGTGGCTG	TGTCCTCTGG	CGAGAGGACC	ACCATCAACT	GCAAGTCCAG	50
F V A V	S L G	E R X	T I N C	K S S	
CCAGAGTATT	TTATACAGCT	CCAACAATCA	AAACTTCTTA	GCTTGGTACC	100
Q S I	L Y S S	N N Q	N F L	A W Y Q	
AGCAGAAACC	AGGACAGCCT	CCGAAGTTGC	TCATTCTACTG	GGCATCTATT	150
Q K P	G Q P	P K L L	I Y W	A S I	
CGGGAATCCG	GGGTCCCTGA	CCGATTCTAGT	GGCAGCGGGT	CTGGGACAGA	200
R E S G	V P D	R F S	G S G S	G T D	
TTTCACTCTC	ACCATCAGCA	GGCTGCAGGC	TGAAGATGIG	GCAGTTTATT	250
F T L	T I S S	L Q A	E D V	A V Y Y	
ACTGTCAGCA	GTATTATAGT	ATTCGGTGCA	CTTTTGGCCA	GGGGACCAAG	300
C Q Q	Y Y S	I P C T	F G Q	G T K	
CTGGAGATCA	AACGAACIGT	GGCTGCACCA	TCGTCTCTTCA	TCTTCCCGCC	350
L E I K	R T V	A A P	S V F I	F P P	
ATCTGATGAG	CCAAGNTTGA	AAATCTGGAA	CTGCTCTCTGT	TGTGTGCGCCT	400
S D E	P X L K	I W N	C L C	C V P C	
GCTTGAATAA	CTTCTATCCC	AGAGANGGCC	AAAGTCCTGT	GGAAGGTGGA	450
L N N	F Y P	R X G Q	S P V	E G G	
TAC	(SEQ ID NO: 28)				453
Y	(SEQ ID NO: 64)				

FIG. 66

E20.19.2MG30.Seq Sequence

10	20	30	40	50
1234567890	1234567890	1234567890	1234567890	1234567890
CTCACTGCA	CTGTCICIG	TGGCICCATC	AGTAGTTACT	NTTGGAGNIG
L T C T	V S G	G S I	S S Y	X W X W
60	70	80	90	100
GATCGGCAG	CCCGNAGGGA	AGGACICGA	GIGCATGGG	TGTTTCTATT
I R Q	P X G	K G L	E W I	G C F Y Y
110	120	130	140	150
ACAGGGGAG	CAOCAAATAC	AACCCCTCCC	TNAAGAGICA	TGICACCATTA
X G S	T N Y	N P S	L K S	H V T I
160	170	180	190	200
TCAGTAGACA	CGICCAAGAA	CCAGTTCTAC	NIGTAGCIGA	GCINTIGIGAC
S V D	T S K	N Q F	Y X K	L S X V T
210	220	230	240	250
CGNIGGGAC	ACGGNCGNCA	ATAACTGNGC	NAGACATAGG	GGAGNAGTGN
X A D	T X X	N N X	A R D	R G X V X
260	270	280	290	300
NNIGGCNINC	TACTINIGACT	ACTGAGGCCA	GNCAACCNIG	GNICACAGTA
W X X	T X T	T E A	X E	P W X T V
310	320	330	340	350
ATCCNTAAGN	CTNNCAANCA	AANGNCGCC	AANGANAC	NNNCTNCC
I X K	X X Q	X X P	X X X	X X X

FIG. 67

### E20.19.2VK.Seq Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCTTTGGTAG	CGNGTCTTGG	CGAGAGGCC	ACCATCAACT	GCAAGTCCAG	50
S L V A	X L G	E R P	T I N C	K S S	
CCAGAGIGTT	TTATACNGCT	CCAAGAATCA	GAACACTTA	GCTTGGTACC	100
Q S V	L Y X S	K N Q	N Y L	A W Y Q	
AGCAGAAACC	AGGACAGCCT	OCTAAGCTGC	TCATTTACTG	GGCATCTACC	150
Q K P	G Q P	P K L L	I Y W	A S T	
CGGGAATCCG	GGGTCCCTGA	CCGATTCAGG	GGCAGCGGGT	CTAGGACAGA	200
R E S G	V P D	R F R	G S G S	R T D	
TTTCACCTCTC	ACCATCAGCA	GCCTGCAGGC	TGAAGATGTG	GCAGTTTACT	250
F T L	T I S S	L Q A	E D V	A V Y F	
TCTGTCACCA	ATATTATAGT	ACTCCGTGGA	CGTTCCGGCA	AGGGACCAAG	300
C H Q	Y Y S	T P W T	F G Q	G T K	
GTGGAAATCA	AACGAACIGT	GGCTGCACCA	TCTGTCTTCA	TCTTCCCGCC	350
V E I K	R T V	A A P	S V F I	F P P	
ATCTGATGAG	CACCTTGAAA	TTCTGGAACT	GCCTCTGNIG	NGTGCCCTGCT	400
S D E	H L E I	L E L	P L X	X A C	
GAACNAACTC	TATCCCCAGA	GANGGCCCAA	AAGTIVCAAG	NNGGNAGGC	450
T N S	I P R	X G P K	V S X	X X G	
NNGATAACGC	CTNITCNCCN	NCNINC	(SEQ ID NO: 30)		476
X I T P	X X X	X	(SEQ ID NO: 66)		

FIG. 68

# 20.20.21MG30.Seq Sequenc

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
AAGCCTTTTC	AGACCNIGCC	CTTCACCTGC	ACTGCTCTCTG	GTCGCTCCAT	50
K P F Q	T X P	F T C	T V S G	G S I	
CAGCAGTGGT	GGTTACTACT	GGAGCTGGAT	CCGCCAGCAC	CCAGGGAAGG	100
S S G	G Y Y W	S W I	R Q H	P G K G	
GCCTGGAGTG	GATTGGGTAC	ATCTATAACA	GTCGGAGCAC	CTACTACAAC	150
L E W	I G Y	I Y N S	G S T	Y Y N	
CCGTCCCTCC	AGAGTCGAGT	TACCATATCA	GTAGACACGT	CTAAGAACCA	200
P S L Q	S R V	T I S	V D T S	K N Q	
GTCTCCCTG	AAGCTGAGCT	CTGTGACTGC	CCCGGACACG	GCCGTGTATT	250
F S L	K L S S	V T A	A D T	A V Y Y	
ACTGTGCGGG	TCAGAAATGG	TCCTACTACT	ACTACTACGG	TATGGACGTC	300
C A G	Q K W	S Y Y Y	Y Y G	M D V	
TGGGGCCAAG	GGACCACGGT	CACCGTCTCC	TNAGCCTCCA	CCAANGGCCC	350
W G Q G	T T V	T V S	X A S T	X G P	
ATCGGTCTTC	CCCTGGCGC	CCTGNTCTAG	GAGCACTCC	CANAGCACAG	400
S V F	P L A P	X S R	S T S	X S T D	
ACGGATNCTG	GGCCTGCCTG	NATCAATGGA	CTACTTTCCC	CGAACCGGTT	450
G X W	A C L	X Q W T	T F P	E P V	
GNNIGTGNNN	CCTGGNAACT	N	(SEQ ID NO: 31)		471
X C X X	W X L		(SEQ ID NO: 67)		

FIG. 69

E-20.22MG30.Seq Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
AAGCCTTNG	AGACCNIGCC	CCTCACTGC	ACTGTCTCTG	GTGGCTOCAT	50
K P X E	T X P	L T C	T V S G	G S I	
CAGTAATTAC	TACTGGAGCT	GGATCOGGCA	GCCCCCAGGG	AAGGGACTGG	100
S N Y	Y W S W	I R Q	P P G	K G L E	
AGTGGATTGG	GTATATCTAT	TACAGTGGGA	GCAOCAAATA	CAACCCCTOC	150
W I G	Y I Y	Y S G S	T N Y	N F S	
CTCAAGAGTC	GAGTCACCAT	ATCAGTAGAC	ACGTCCAAGA	ACCAGTCTTC	200
L K S R	V T I	S V D	T S K N	Q F S	
CCTGAAGCTG	AGCTCTGIGA	COGCTGCGGA	CACGGCOGTG	TATTACTGIG	250
L K L	S S V T	A A D	T A V	Y Y C A	
CGAGAGGGCC	CGGGGGGAGC	TACTACTACT	ACGGTATGGA	CGTCTGGGGC	300
R G P	G G S	Y Y Y Y	G M D	V W G	
CAAGGGACCA	CGGTACCGT	CTOCTCAGCC	TCCACCAAGG	GOCCATCGGT	350
Q G T T	V T V	S S A	S T K G	P S V	
CTTCCCCCTG	GCGCCCTGCT	CCAGGAGCAC	CTCCGAGAGC	ACAGCGGGCC	400
F P L	A P C S	R S T	S E S	T A A L	
TGGGCTGGCT	GGGTCAAGGA	CTACTTCCCC	GAACCGGIGA	CGGTGTTCGN	450
G C L	G Q G	L L P R	T G D	G V R	
NGGAC	(SEQ ID NO: 32)				456
X N	(SEQ ID NO: 68)				

FIG. 70

# Amino Acid Sequences and Structure of Human Heavy Chain Derived from EGFR-Specific Hybridomas

Human $\gamma 2$	CDR1	CDR2	CDR3	ASTKGPSVPPLAPCSRSTST	(SEQ ID NO: 73)
4-31	VSGGSISSQDYTNEMIRQHPGKGLNIGIYITSGFTYTPSLKSRVTLSVDTSNQPSLKLSSTVAADTAVTYCAR				(SEQ ID NO: 35)
1.1	D	DC		STVNPG WFDP	(SEQ ID NO: 31)
E2.4	D	S	H-P	NIVTGG AFDI	(SEQ ID NO: 41)
E2.5	D	S	H	KPVVGG EDY	(SEQ ID NO: 43)
E6.2	D	DP		ESLYTGG GMDV	(SEQ ID NO: 45)
E6.4	DM-D	S	H	GVVTTY YFDY	(SEQ ID NO: 47)
E20.21	C			QKWSYTYTGMDV	(SEQ ID NO: 75)

Human $\gamma 2$	CDR1	CDR2	CDR3	ASTKGPSVPPLAPCSRSTST	(SEQ ID NO: 73)
4-61	VSGGSISSQDYTNEMIRQHPGKGLNIGIYITSGFTYTPSLKSRVTLSVDTSNQPSLKLSSTVAADTAVTYCAR				(SEQ ID NO: 38)
E2.11	D	HL	H	DPLTGGP FDY	(SEQ ID NO: 49)
E6.3	D	S	H	DSILGA TNY	(SEQ ID NO: 51)
E7.6.3	D	S	H	V-DRTVCA FDI	(SEQ ID NO: 53)

FIG. 71

E7.5.2.K.aa Sequence

10	20	30	40	50
1234567890	1234567890	1234567890	1234567890	1234567890
CTGTCIGCAT	CTGTAGGACA	CAGAGTCATA	ATCACTIGCC	GGCAAGTCA
50				
L S A S	V G D R	V I I T	C R A S	Q
AAACATCACC	GAACATTATA	ATTGGTATCA	GCAGATAGCA	GGAAAAGCCC
100				
N I T D	H L N W	Y Q Q I	A G K A	P
CTAGGCCCT	GATATACACT	GCATCCAGTT	TGCAAGGIGG	GGTCCCATCA
150				
R P L I	Y T A S	S L Q G	G V P S	
AGGTTCAGIG	GCAGIGGATC	TGGACAGAT	TTCATCTCA	CCATCAGCAG
200				
R F S G	S G S G	T D F T	L T I S	S
TCGTCAACCT	GAACATTTTT	CAACTTACTA	CTGCAACAG	AGTTACAGTA
250				
L Q P E	D F S T	Y Y C Q	Q S Y S	T
CCCCGIGCAG	TTTTGGCCAG	GGGACCAAGC	TGGAGATCAA	ACGAAGTIG
300				
P C S F	G Q G T	K L E I	K R T V	
GCTGCACCAT	CTGTCTTCAT	CTTCCCGCCA	TCGTATGAGC	AGTTGAATC
350				
A A P S	V F I F	P P S D	E Q L K	S
TGGAAGTCC	TCGTGTGIGT	GCTGCGCIGAA	TAACTTCTAT	CCCA
394				
G T A S	V V C L	L N N F	Y P	

FIG. 72

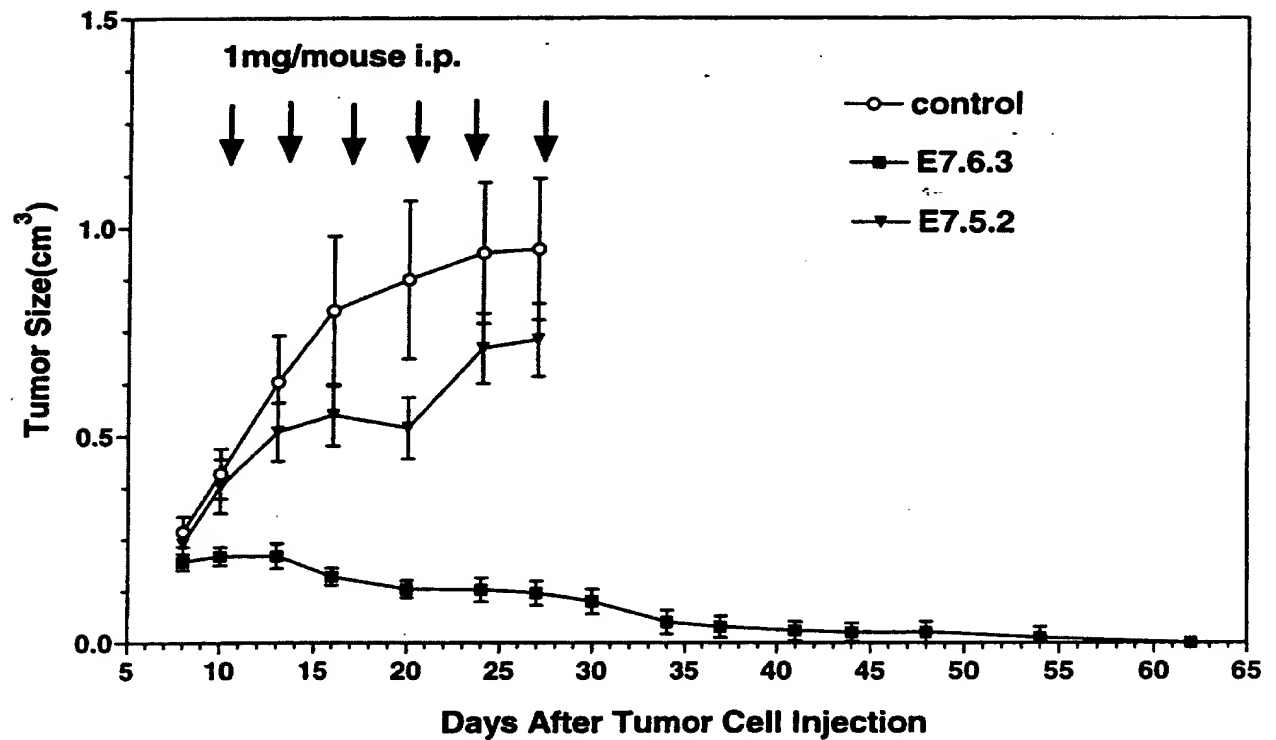


# E7.5.2.v.aa Sequence

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GTGAAGGTCCT	CCTGCAAGGC	TTCTGGATAC	ACCTTCAGCG	GCTACTATAT	50
V K V S	C K A	S G Y	T F S G	Y Y M	
GCCTGGGGTG	CGACAGGCC	CTGGACAAGG	GCTTGAGTGG	ATGGGATCGA	100
H W V	R Q A P	G Q G	L E W	M G S I	
TCCACCCCTAA	CAGTGGTGGC	ANAACTTTG	CACAGAAGTT	TCAGGGCAGG	150
H P N	S G G	X N F A	Q K F	Q G R	
GTCACCATGA	CCAGGGACAC	GTCCATCAAC	ACAGCCTACT	TGGAGCTGAG	200
V T M T	R D T	S I N	T A Y L	E L S	
CAGGCTGAGA	TCTGACGACA	CGGCCGTGTA	TTACTGTGCG	AGAGATAAAA	250
R L R	S D D T	A V Y	Y C A	R D K N	
ACTACGGTGA	CTACGTCCTT	GACTATTGGG	GCCAGGGAAC	CCTGGTCACC	300
Y G D	Y V F	D Y W G	Q G T	L V T	
GTCTCTCAG	(SEQ ID NO: 34)				310
V S S	(SEQ ID NO: 70)				

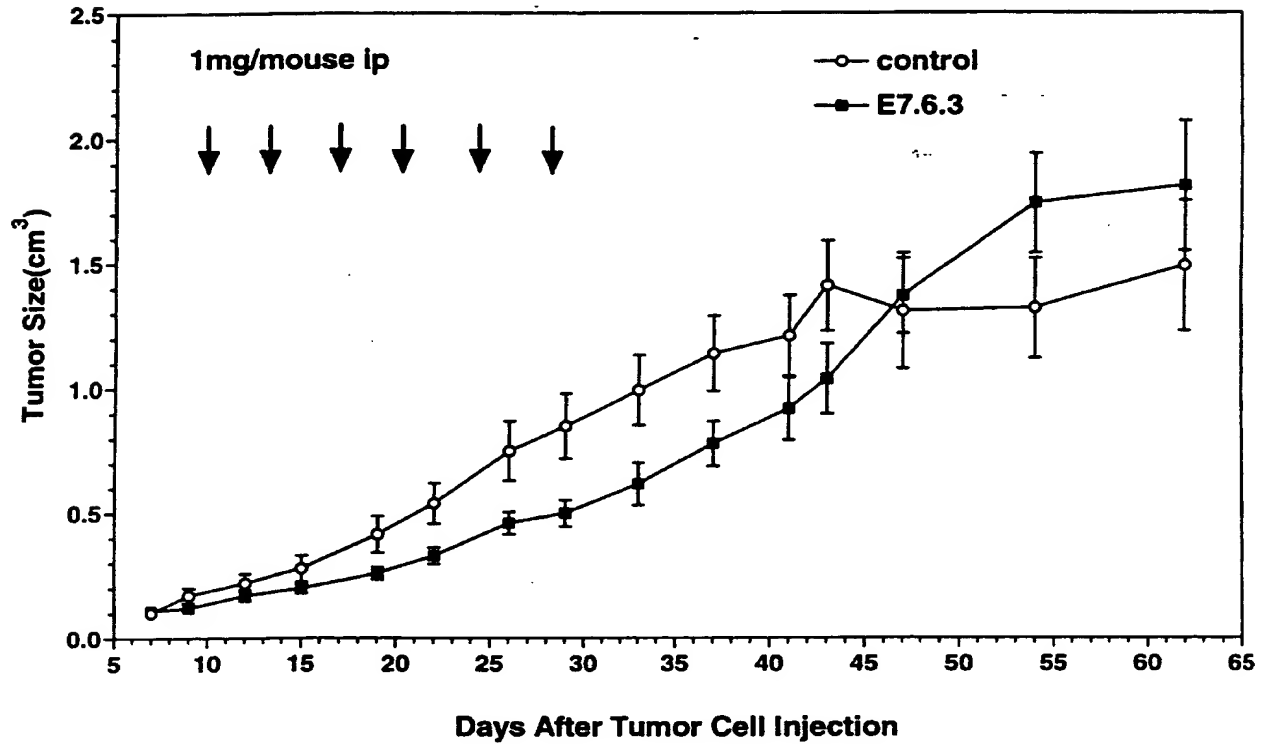
FIG. 73

# **Effect of E7.6.3 or E7.5.2 on human epidermoid carcinoma A431 growth in nude mice**



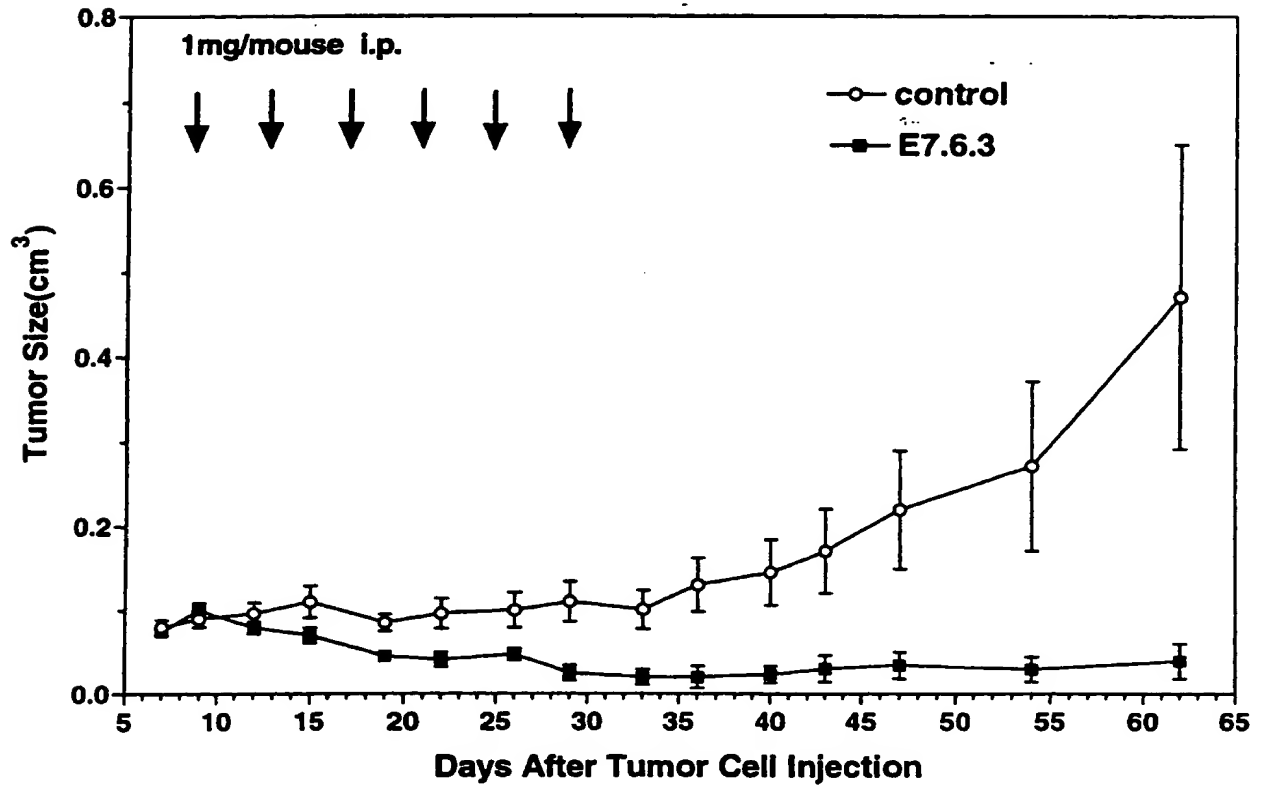
**FIG. 74**

**Effect of E7.6.3 on human pancreatic carcinoma HPAC  
growth in nude mice**



**FIG. 75**

**Effect of E7.6.3 on human pancreatic carcinoma BxPC-3 growth in nude mice**



**FIG. 76**

### Effect of E7.6.3 on HS766T Pancreatic tumor growth in nude mice

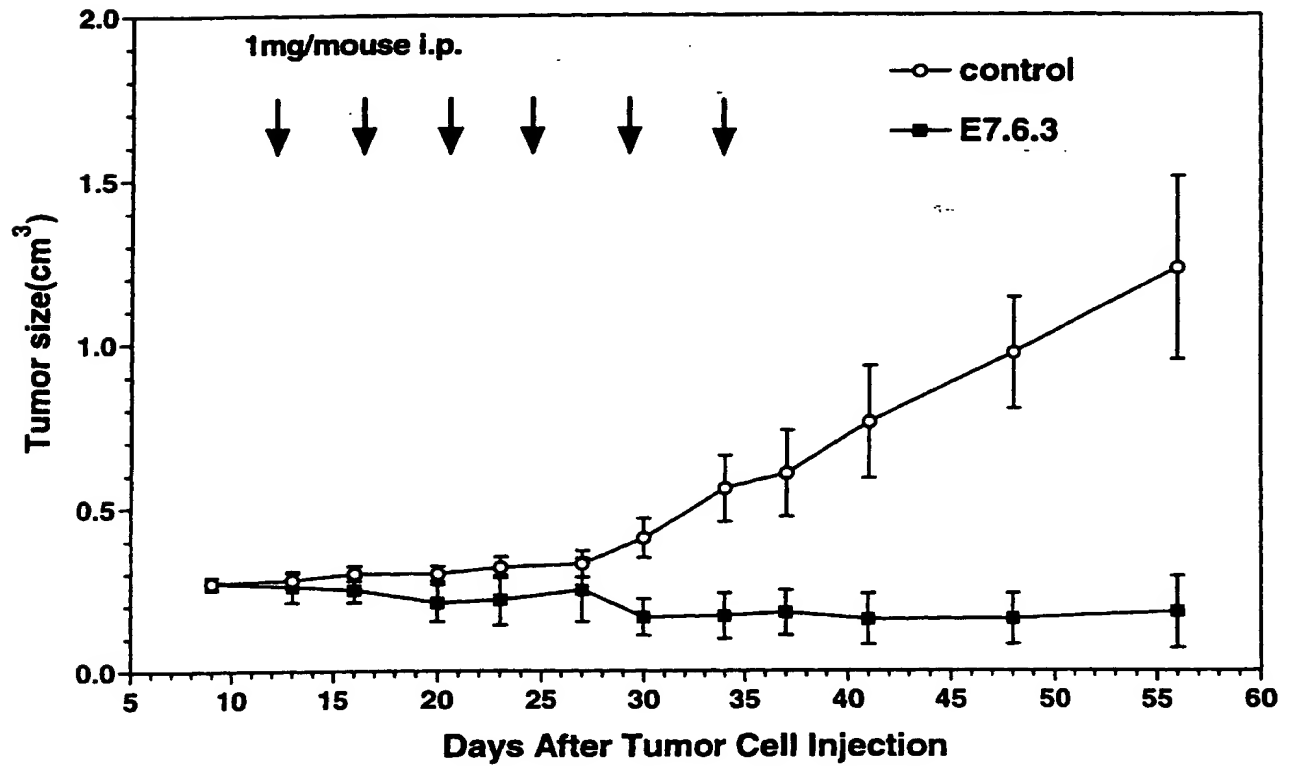
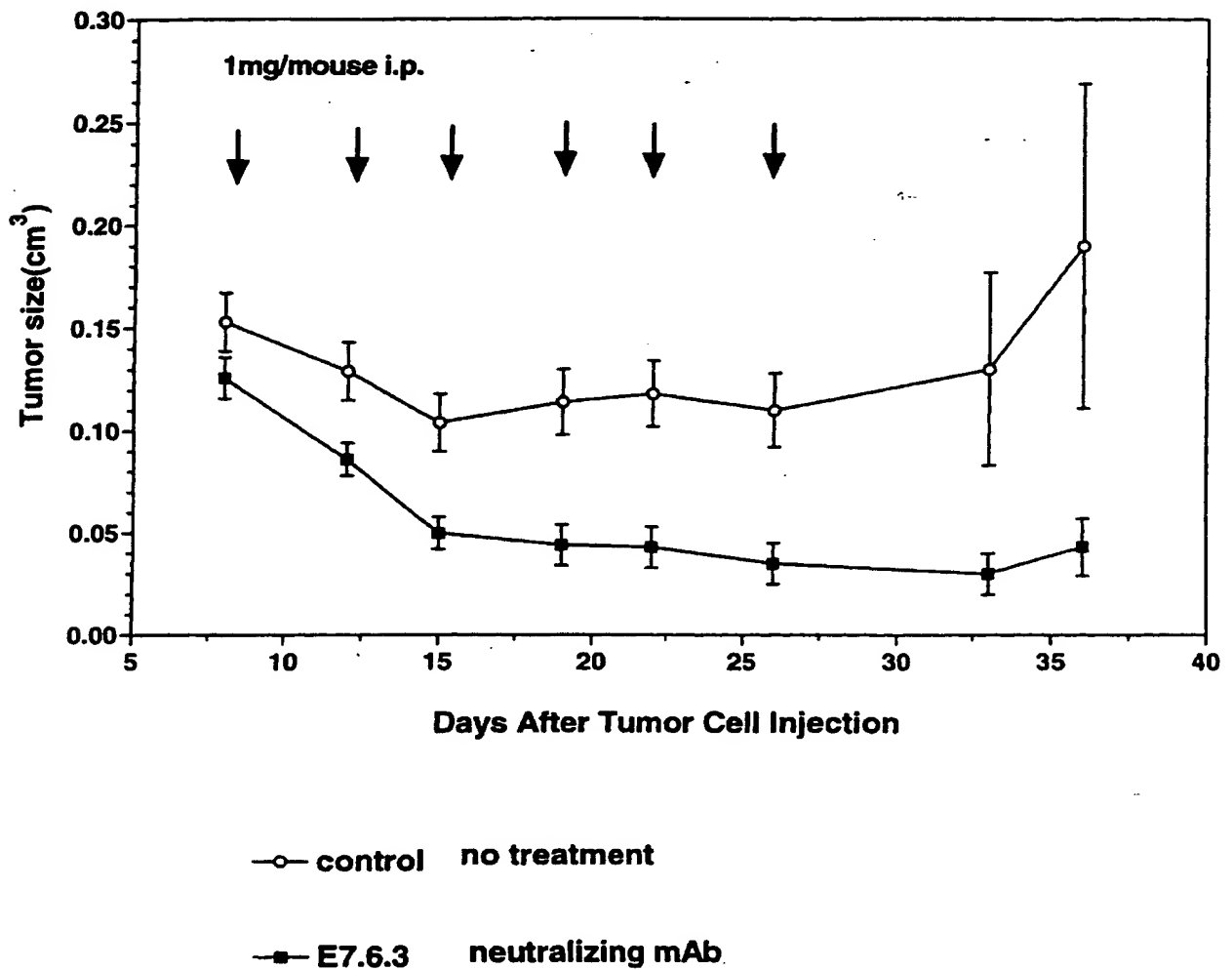


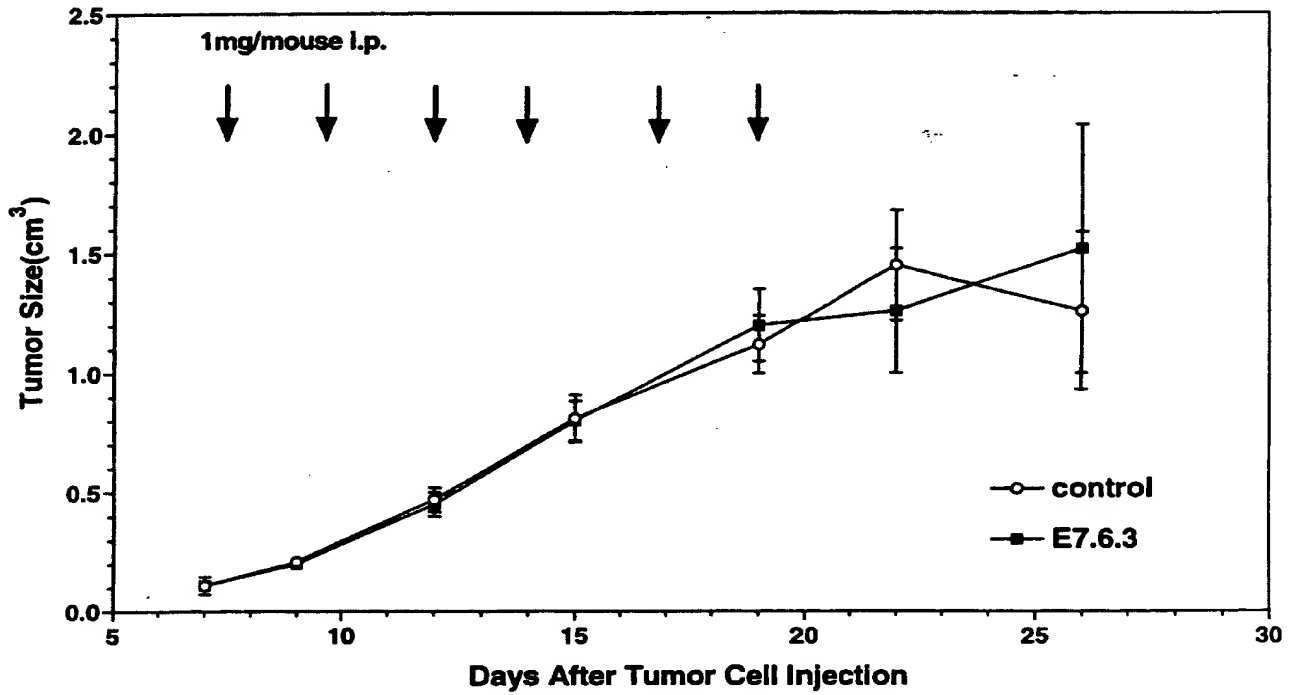
FIG. 77

**Effect of E7.6.3 on SK-RC-29 human kidney carcinoma growth in nude mice**

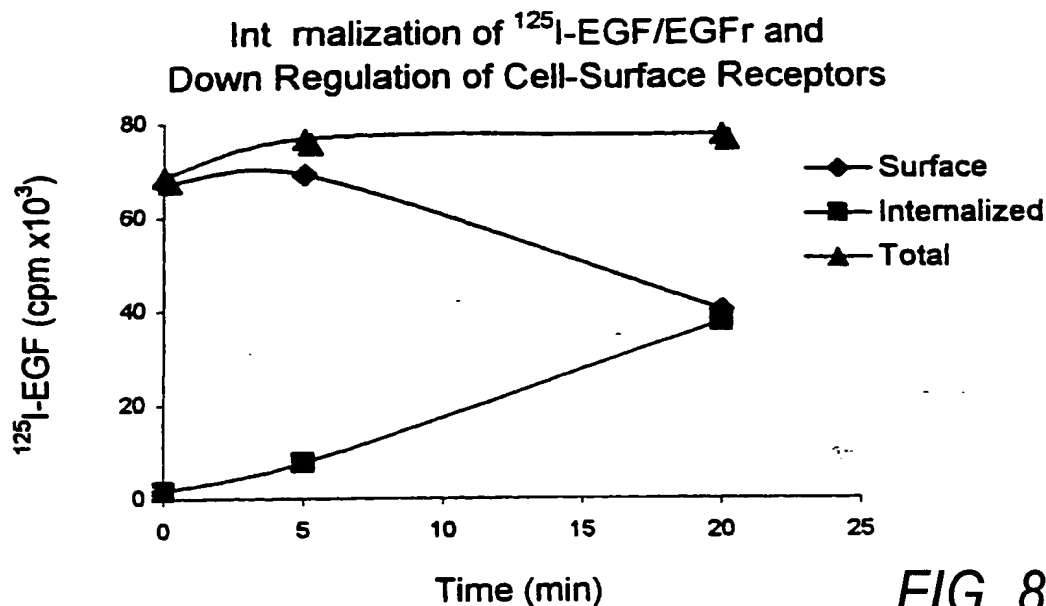


**FIG. 78**

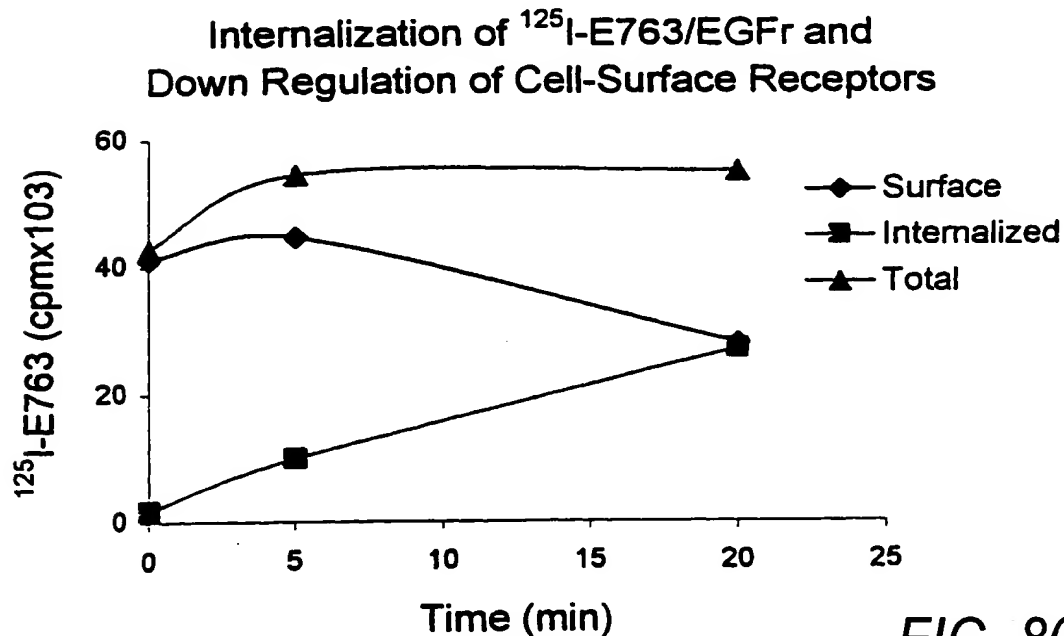
**Effect of E7.6.3 on human colon carcinoma  
SW707 (EGFr-) growth in nude mice**



**FIG. 79**



$^{125}\text{I}$ -EGF	Time (min)	Surface	Internalize	Total	% internalized
	0	67.153	1.515	68.668	2.2
	5	68.997	7.649	76.646	10
	20	39.986	37.406	77.392	48

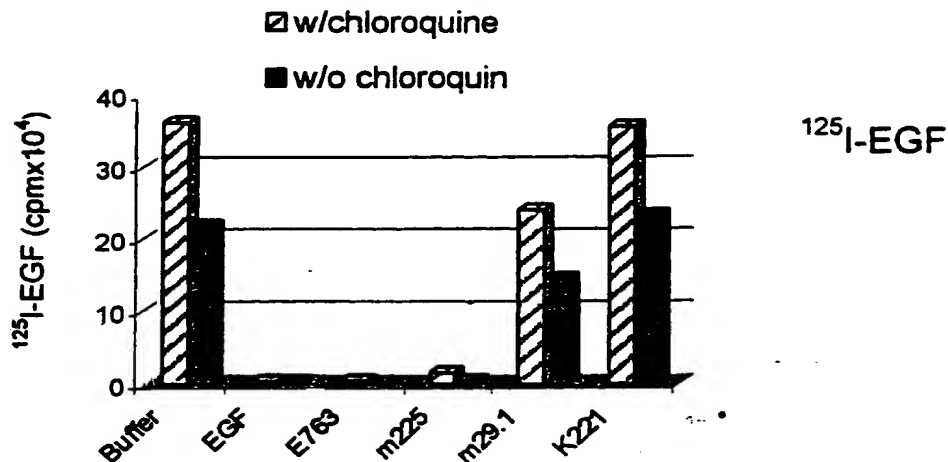


$^{125}\text{I}$ -E763	Time (min)	Surface	Internalize	Total	% internalized
	0	41.051	1.684	42.735	3.9
	5	44.567	9.876	54.443	18
	20	27.969	26.998	54.967	49



# Degradation of $^{125}\text{I}$ -EGF or $^{125}\text{I}$ -E76.

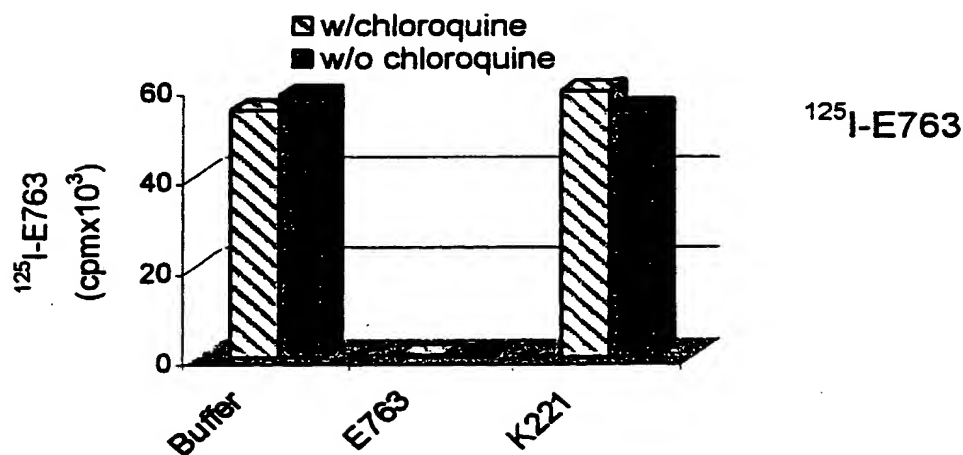
A431 c



w/ or w/o chloroquine (100  $\mu\text{M}$ )

		w/chloroq	w/o chloroquine	% degradation	% competition
cpm $\times 10^4$	Buffer	36.0898	21.8277	40	0
	EGF	0.3684	0.3776		98
	E763	0.481	0.2132		99
	m225	1.5468	0.4882		98
	m29.1	23.9704	14.459		34
	K221	35.5084	23.2694	34	1.6

FIG. 81A



w/ or w/o chloroquine (100  $\mu\text{M}$ )

		w/chloroq	w/o chloroquine	% degradation	% competition
cpm $\times 10^4$	Buffer	54.608	57.824	0	0
	E763	0.536	0.441		99
	K221	58.956	54.83	7	5

FIG. 81B

## Effects of E763 and m225 on EGFr degradation

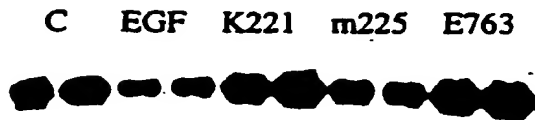


FIG. 82A



FIG. 82B

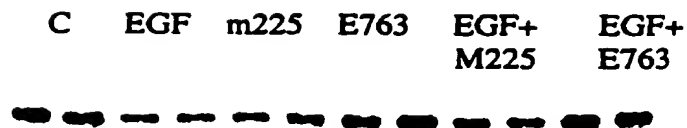


FIG. 82C

Effect of E763 and m225 on EGFr threonine phosphorylation

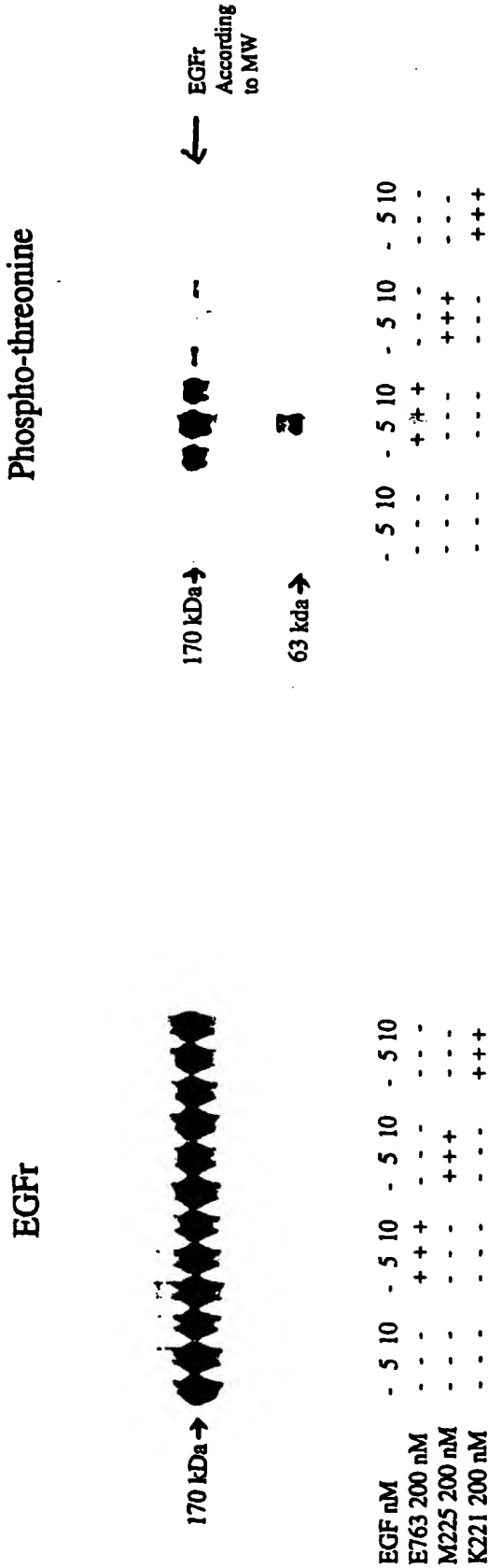


FIG. 83A

FIG. 83B

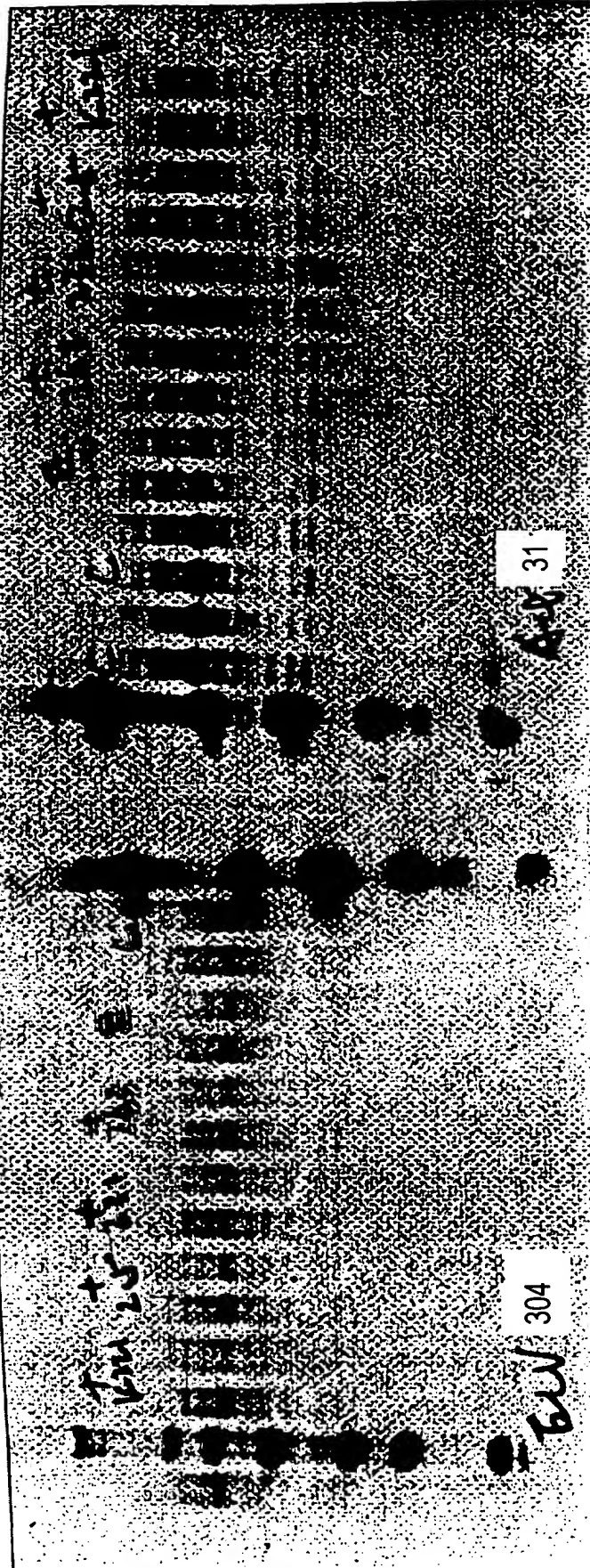
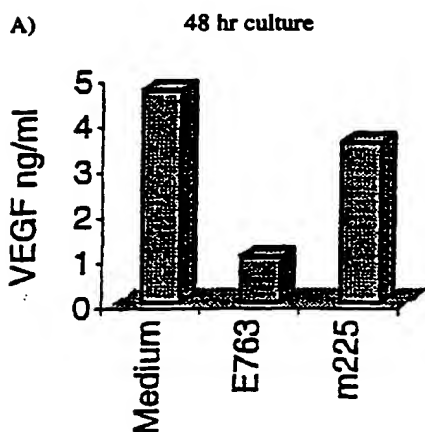


FIG. 84

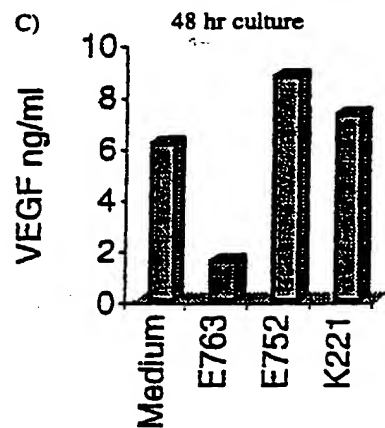
## E763 on VEGF secretion

**Effects of E763 and m225 on VEGF secretion in cultured A431 cells**



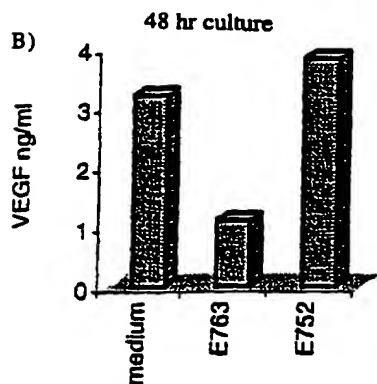
**FIG. 85A**

**Effects of E763 and E752 on VEGF secretion in cultured A431 cells**



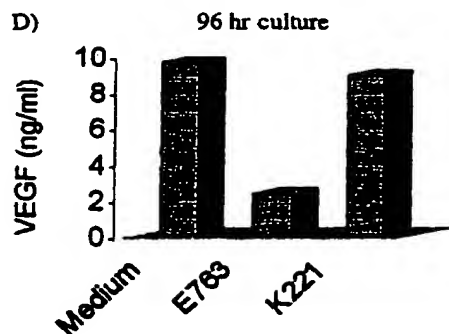
**FIG. 85B**

**Effects of E763 and E752 on VEGF secretion in cultured A431 cells (24 hr)**



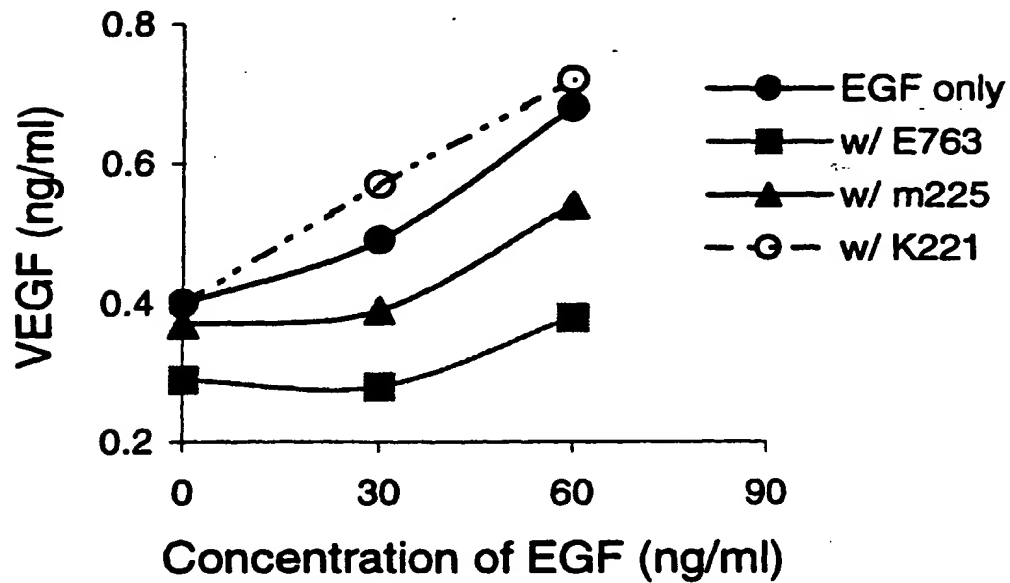
**FIG. 85C**

**Effect of E763 on VEGF secretion in cultured A431 cells**



**FIG. 85D**

## Effects of E763 and m225 on VEGF secretion in cultured endothelial cells



11/5/98 VEGF in endothelial cells (ECV304)(ATTCC, CRL-1998)  
 VEGF ng/ml no serum

	0	30	60
EGF only	0.4	0.49	0.68
w/ E763	0.29	0.28	0.38
w/ m225	0.37	0.39	0.54
w/ K221	0.4	0.57	0.72

FIG. 86